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# **HEALTH PROBLEMS OF FINNISH TRAVELLERS:**

## **FOCUS ON INFECTIONS**

**Heli Siikamäki**

ACADEMIC DISSERTATION

To be publicly discussed,  
with the permission of the Faculty of Medicine of the University of Helsinki,  
in Lecture Hall 4, Meilahti Hospital, Haartmaninkatu 4, Helsinki,  
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*To my mother*



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## ABBREVIATIONS

ACT	artemisinin-based combination therapy
AFTA	Association of Finnish Travel Agents
BCI	Bayesian credible interval
CDC	Centers for Disease Control and Prevention
G6PD	glucose-6-phosphate dehydrogenase
HIV	human immunodeficiency virus
NIDR	National Infectious Disease Register
OSF	Official Statistics of Finland
PCR	polymerase chain reaction
RDT	rapid diagnostic test
STD	sexually transmitted disease
TD	traveller's diarrhoea
VFR	visiting friends and relatives
WHO	World Health Organization



## LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

- I Siikamäki H, Kivelä P, Fotopoulos M, Ollgren J, Kantele A. Illness and injury of travellers abroad: Finnish nationwide data 2010–2012 with incidences in various regions of the world. Submitted.
- II Siikamäki H, Kivelä P, Sipilä P, Kettunen A, Kainulainen K, Ollgren J, Kantele A. Fever in Travelers Returning from Malaria-Endemic Areas: Don't Look for Malaria Only. *J Travel Med.* 2011;17:400–4.
- III Guedes S, Siikamäki H, Kantele A, Lyytikäinen O. Imported Malaria in Finland 1995–2008: An Overview of Surveillance, Travel Trends, and Antimalarial Drug Sales. *J Travel Med.* 2010;18:239–44.
- IV Siikamäki H, Kivelä P, Lyytikäinen O, Kantele A. Imported malaria in Finland 2003–2011: prospective nationwide data with rechecked background information. *Malar J.* 2013 Mar 14;12:93.

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## ABSTRACT

The number of international travellers has increased substantially during recent decades. Along with this, the number of travel-related health problems, both during and after travel, has also increased. This thesis addresses illness and injury in Finnish travellers, with its focus on infections. The main aim was to find tools for risk-assessment, pre-travel advice, and post-travel examination of travellers.

The specific aims were (1) to provide a comprehensive overview of illness and injury of Finnish travellers diagnosed while abroad, and to calculate the incidences in various geographic regions and countries, (2) to define the causes of fever in returning travellers and to improve clinical differential diagnostics, (3) to identify risk groups for imported malaria in Finland, and (4) to analyze in detail the risk groups for imported malaria, and to explore whether *Plasmodium falciparum* infection can be contracted despite appropriate chemoprophylaxis.

Study I analyzed data on Finnish travellers with health problems abroad during 2010–2012, retrieved from the database of an assistance organization of insurance companies (SOS International) covering approximately 95% of all Finnish cases requiring aid abroad. These data were compared to numbers of Finnish travellers retrieved from the database of the Official Statistics of Finland (OSF) in order to calculate the incidences of illness and injury at various destinations. The SOS database included 50 710 cases: 85% outpatients and 16% inpatients. The most common diagnostic category was infections (60%), followed by injuries (14%). The most common diagnoses were acute gastroenteritis (23%) and respiratory infections (21%). Overall incidence of illness or injury was high in Africa, southern Europe plus the eastern Mediterranean, and Asia. Incidence of infections was high in Africa, yet it was also high in southern Europe plus the eastern Mediterranean and Asia. Incidence of injuries was highest in southern Europe plus the eastern Mediterranean and Asia. This study shows that pre-travel counselling is necessary also for travel to southern Europe, and that means for prevention of gastrointestinal and respiratory infections in travellers need development.

Study II explored the final diagnoses of returning travellers with fever. The study included 462 febrile adults who, after travelling in malaria-endemic areas, were admitted during 2005–2009 to the Helsinki University Central Hospital emergency room; their medical records were studied retrospectively. The most common diagnostic categories were acute diarrhoeal disease (27%), systemic febrile illness (15%), and respiratory illness (15%). One traveller in four had a potentially life-threatening illness; septicemia was as common as malaria (5% vs. 4%). One in ten had more than one newly-acquired diagnosis. Only 42% of those fulfilling

the criteria of influenza-like illness were tested; their nasal swabs for influenza A and B antigen were positive in 15%. The proportion of HIV cases (1% of all patients) exceeded its prevalence in the population for which routine HIV testing is recommended. These data show the importance of careful diagnostics in cases of febrile returning travellers, suggesting that in a tertiary hospital, the diagnostic protocol for fever without localizing symptoms in a traveller returning from malaria-endemic area should – in addition to malaria smears – include blood cultures, an influenza rapid diagnostic test, and an HIV test.

Study III analyzed surveillance data on malaria cases reported to the National Infectious Disease Register in Finland 1995–2008, and related them to travel statistics and antimalarial drug sales. A total of 484 cases were reported (incidence, 0.7/100 000 population). Infections were mostly acquired in Africa (76%). The most common species were *Plasmodium falciparum* (61%) and *P. vivax* (22%). During 2000–2008, travel to malaria-endemic areas increased, yet no increase occurred in malaria cases, and a decreasing trend occurred in the number of antimalarial drug sales. Of all cases, 283 were Finnish-born and 201 foreign-born. Of all cases, 15% were children, 72% of them foreign-born. Among those foreign-born, for 89%, the infection was acquired in the region of birth, implying that immigrants visiting friends and relatives (VFR travellers) are a risk group on which effort in disseminating pre-travel advice should focus.

Study IV analyzed in detail the background information of all malaria cases diagnosed in Finland 2003–2011, a total of 265 cases (incidence 0.5/100,000 population): 54% were born in malaria-endemic countries, 86% were currently living in non-endemic regions. Malaria was most commonly contracted in sub-Saharan Africa (81%). *Plasmodium falciparum* proved to be the most common species (72%). Immigrants constituted the largest group (44%). Of those born in endemic regions, 20% had received pre-travel advice, compared with 81% of those born in non-endemic regions. Of those with *P. falciparum*, 4% reported regular use of appropriate chemoprophylaxis; individual rechecking revealed, however, that none had been fully compliant. The data suggest that mefloquine, atovaquone/proguanil, and doxycycline are effective as chemoprophylaxis against *P. falciparum* malaria, when taken conscientiously.



# 1 INTRODUCTION

We no longer live isolated from other countries: we travel because of leisure, work, education, and migration. International travel has, in recent decades, increased substantially: the annual number of international tourist arrivals worldwide reached 1 000 million in 2012, and by 2030 is expected to reach 1 800 million. Travel to emerging economies in Asia and the Pacific, followed by Africa, is expected to increase at double the pace of travel to advanced economies,<sup>1</sup> with the need for health care during travel expected to increase accordingly. Over half the travellers to developing countries are estimated to fall ill during their trip,<sup>2</sup> and 8% to require medical attention.<sup>2,3</sup> Few data have been published on travel to developed countries. The escalating numbers of travellers cause a rising burden on health care systems both in the host countries during travel and in the countries of origin after their return. Infectious diseases do not recognize borders: with travellers, epidemics may spread from one country to another. Increasing international travel is also reflected as rising numbers of imported infectious diseases in Europe, among them, severe, life-threatening diseases.<sup>4,5</sup>

Travel medicine is a relatively newly established medical specialty which covers a broad spectrum of issues: epidemiology of travel-related health problems, risk-assessment, and pre-travel advice, as well as post-travel diagnostics and treatment. Travel medicine overlaps tropical medicine, infectious diseases, general medicine, public health, epidemiology, migration medicine, and global health. Many studies have recorded health problems of travellers after their return diagnosed in specialized travel medicine clinics or referral centres, whereas only limited data has been focused on illness and injury diagnosed during travel abroad.

Among international travellers, Europeans represent the largest group.<sup>1</sup> Finland is among the few countries that monitor the annual numbers of their travellers to various destinations. The number of international travellers has more than doubled during the last decade, and Finns, with a population of 5.4 million inhabitants, made 7.7 million at-least-overnight trips abroad in 2012,<sup>6</sup> the majority of them to nearby regions, but considerable numbers also to tropical and sub-tropical regions.

This thesis addresses the illness and injury of Finnish travellers, with a focus on infections. It aims at a comprehensive overview of illness and injury of travellers diagnosed while abroad, and an estimation of health risks in various geographic regions during travel. It also focuses on life-threatening infections after travel by exploration of causes of fever in returning travellers, and by analysis of all malaria cases diagnosed in Finland 1995–2011.

## 2 REVIEW OF THE LITERATURE

### 2.1. ILLNESS AND INJURY OF TRAVELLERS

Along with expansion of international travel, data on the illness and injury of travellers has become increasingly important.<sup>7,8</sup> Reporting and surveillance of travel-related illnesses is of public-health importance. An epidemic may spread across international borders along with travellers,<sup>7–10</sup> returned travellers may serve as sentinels of an outbreak or epidemic,<sup>11</sup> and recognition of disease may lead to measures to limit the transmission in the country of the travel.<sup>12–14</sup> Epidemiological data on travellers' health problems constitute an evidence-base for health recommendations to travellers.<sup>3,15</sup> Such data are necessary for risk-assessment when prioritizing preventive measures for an individual traveller in pre-travel counselling,<sup>16–18</sup> and benefit clinicians who must consider possible differential diagnoses after travel.<sup>19,20</sup>

#### 2.1.1. ESTIMATING HEALTH RISKS RELATED TO TRAVEL

Several research approaches have been used for estimating risk for illness or injury during travel: case reports, case series,<sup>21–23</sup> chart reviews<sup>24–27</sup> case-control studies,<sup>28–32</sup> cross-sectional studies often performed as airport surveys,<sup>33–46</sup> prospective cohort studies,<sup>2,3,47–56</sup> use of notification data,<sup>57–62</sup> and sentinel-surveillance data.<sup>4,12,63–75</sup> The classification of diseases used in the studies varies, making comparisons difficult. Leder *et al* have made a comparative analysis of the methodological approaches used<sup>19</sup> and concluded that each approach has its strengths, limitations, and biases, which considerably affect the risk estimates and generalizability of the results. Steffen<sup>3,15,76,77</sup> has presented calculations of the estimated incidence of travellers' health problems in developing countries per month abroad; these figures have served as the basis for many risk estimates in travel medicine.<sup>19</sup> GeoSentinel, a multicentre surveillance network reporting mainly post-travel health problems, uses proportionate morbidity: the number of travellers with a given diagnosis divided by the total number of ill travellers.<sup>19,68,74,78</sup> The main limitation in all these studies is the lack of numbers of those travelling to the destinations,<sup>19</sup> which may cause distortion in the proportions of health problems. Travel statistics have served as denominator data to estimate the incidence of single imported diseases.<sup>60,61,79,80</sup> Data providing comprehensive numerator and denominator data for calculation of incidence of the whole spectrum of travellers' health problems are, however, lacking.<sup>19</sup>

## 2.1.2. ILLNESS AND INJURY DURING TRAVEL

### ILLNESS DURING TRAVEL

#### *Cross-sectional and prospective studies*

Cross-sectional and prospective studies have shown that 12 to 70% of travellers, depending on destinations and the traveller population, encounter health problems during travel<sup>2,3,33–37,47,49–53,81,82</sup> (Table 1). Various studies report 3 to 11% of travellers as seeking medical care,<sup>2,3,33,34,37,47,49,50,52,53,81</sup> and 0.1 to 0.5% to be hospitalized while abroad.<sup>2,3,50,52,53</sup> A study on Israeli travellers<sup>51</sup> has reported an exceptionally high proportion (70%) of travellers with health problems; 33% sought medical care and 4% needed hospital treatment during travel. The authors attributed these findings to the demographic profile of their travellers. They were younger and travelled for longer periods of time and in more primitive settings than did those in the other studies.

#### *Risk factors for illness during travel*

Young age<sup>3,37,47,49,52,53</sup> and long duration of travel<sup>2,3,33,49,51–53</sup> have both been reported as risk factors for illness during travel. Among studies, the overall frequency of health problems and that of specific symptoms has varied according to travel destination and geographic area visited.<sup>2,3,33–37,49,52,53,82</sup> Most of the studies have been done on those travelling from developed to developing countries.<sup>2,3,36,47,51,52</sup> Health problems associated with travel to or within Europe have been studied less<sup>4,34,53,82</sup>; rates of illness have shown regional differences, with the highest rates in travellers to the Mediterranean countries<sup>34,82</sup> or eastern Europe.<sup>4,82</sup> Other factors reported as associated with increased risk for health problems abroad include reason for travel,<sup>3,33,34</sup> living among the local population,<sup>3</sup> adventure tourism,<sup>3,49</sup> travelling under primitive conditions,<sup>52</sup> poor travel preparation,<sup>82</sup> inexperience in travel,<sup>37</sup> poor compliance with food hygiene,<sup>51</sup> travel with friends rather than family,<sup>51</sup> travel alone,<sup>51</sup> female gender,<sup>2</sup> and various pre-existing medical conditions.<sup>53</sup>

#### *Types of illness during travel*

All studies have reported diarrhoea as the most frequent health problem (11–59%) encountered during travel.<sup>2,3,33–37,47,49–53,81,82</sup> Respiratory infections rank second (2–26%).<sup>2,3,33–37,49–53,81</sup> Skin problems<sup>2,3,35,47,52,82</sup> and fever<sup>2,3,47,50,52</sup> are among the next most commonly reported.

**Table 1** Studies on health problems of Western travellers during travel

First author, country, publication year	Study population	Recruitment and method of data collection	N	Reported health problems during travel, % of all	Sought medical care during travel, % of all	Hospitalized, % of all	Accidents or injuries, % of all	Most common illnesses during travel, % of all
Kendrick, <sup>33</sup> USA, 1972	US residents returning from international travel	at four airports; questionnaire	26 119	22	6	NA	NA	gastroenteritis, 15 upper respiratory infection, 7
Kendrick, <sup>34</sup> USA, 1972	US residents ≥18 years old returning from Europe	at one airport; questionnaire	9 492	20	4	NA	NA	gastroenteritis, 11 upper respiratory infection, 10
Reid, <sup>35</sup> UK, 1980	travellers returning to UK	at airport or by travel agent; questionnaire	2 211	43	NA	NA	NA	gastrointestinal symptoms, 39 respiratory symptoms, 7
Peltola, <sup>36</sup> Finland, 1983	travellers returning from Spain, North Africa, Thailand, or around-the world-trip	on return flights; questionnaire	2 665	48	NA	NA	NA	diarrhoea, 18 upper respiratory symptoms, 10 sunburn, 10
Steffen, <sup>3</sup> Switzerland, 1987	travellers ≥12 years old visiting developing countries for ≤90 days	when boarding for trip; questionnaire pre-travel and 7 months after departure; infections confirmed by clinician	10 524	15	8	0.5	0.5	gastrointestinal symptoms, 13 common cold, 2 fever, 2 dermatosis, 2
Cossar, <sup>37</sup> Scotland UK, 1990	travellers returning to Scotland	cumulative review of studies; several recruitment methods; questionnaire	13 816	36	3	NA	NA	gastrointestinal symptoms, 28 respiratory symptoms, 4
Getz, <sup>47</sup> Norway, 1990	travellers ≥10 years old visiting developing countries; clients of one travel clinic	when seeking pre-travel advice; questionnaire pre-travel and 1 month post-travel	313	35	7	NA	NA	diarrhoea, 59 exhaustion, 28 sunburn, 21 common cold, 14 insomnia, 12 fever, 9 skin problems, 2 headache, 7
Ahlm, <sup>49</sup> Sweden, 1994	travellers ≥10 years old visiting both developed and developing countries; clients of one travel clinic	when seeking pre-travel advice; questionnaire completed during travel	442	49	9	NA	7	diarrhoea, 36 upper respiratory infection, 21 more than one illness, 14



First author, country, publication year	Study population	Recruitment and method of data collection	N	Reported health problems during travel, % of all	Sought medical care during travel, % of all	Hospitalized, % of all	Accidents or injuries, % of all	Most common illnesses during travel, % of all
Bruni, <sup>50</sup> Switzerland, 1997	travellers ≥13 years old visiting countries outside western Europe travelling for ≤13 weeks; clients of one travel clinic	when seeking pre-travel advice; questionnaire 2 weeks after return	2 109	38	11	0.3	1.3	diarrhoea, 26 common cold, 13 fever, 11
Scoville, <sup>81</sup> USA, 1997	travellers visiting both developed countries; clients of one travel clinic	when seeking pre-travel advice; questionnaire	271	39	9	NA	NA	diarrhoea, 23 upper respiratory infection, 19
Hill, <sup>2</sup> USA, 2000	travellers visiting developing countries travelling for ≤90 days; clients of one travel clinic	when seeking pre-travel advice; questionnaire returned within 2 weeks after return, telephone interview of those reporting illness; follow-up of all after 2 months	784	64	8	0.2	4	diarrhoea, 46 respiratory tract symptoms, 26 skin problems, 8 high altitude illness, 6 motion sickness, 5 febrile episodes, 3
Evans, <sup>82</sup> UK, 2001	package holiday tourists travelling in Europe	at one airport; questionnaire 2 weeks after return	1 469	65	NA	NA	NA	diarrhoea, 26 sunburn, 25 respiratory infection, 8
Winer, <sup>51</sup> Israel, 2002	travellers visiting developing countries; clients of one travel clinic	when seeking pre-travel advice; pre-travel questionnaire and post-travel telephone interview	200	70	33	4	7	gastrointestinal symptoms, 30 respiratory tract symptoms, 18
Rack, <sup>52</sup> Germany, 2005	travellers ≥18 years old visiting developing countries for <2 months; clients of one travel clinic	when seeking pre-travel advice; questionnaire after return	658	43	7	0.5	5	gastrointestinal illness, 35 respiratory illness, 14 fever, 6 dermatologic illness, 4 more than one illness, 10
Fleck, <sup>53</sup> Germany, 2006	travellers visiting Europe and outside Europe; clients of one insurance company	recruited by insurance company; pre-travel questionnaire, post-travel telephone interview	1 471	12	3	0.1	2	Overseas gastrointestinal symptoms, 11 respiratory diseases, 3 Europe gastrointestinal symptoms, 2 respiratory diseases, 2

NA = non-applicable

*Consequences of illness during travel*

Illness during travel has been reported to cause incapacitation or confinement to bed in 14 to 24% of travellers<sup>37,49,50</sup> for a mean of 2–3 days.<sup>49,50</sup> In one Swedish study, the mean duration of illness was 4.5 days<sup>49</sup>; one Swiss study has calculated incapacitation to cause a loss of 2% of total time abroad.<sup>50</sup> A Norwegian study has reported 11% to have changed plans because of illness with a mean of 3.5 travel days lost, and 8% to have felt that illness made their travel less enjoyable.<sup>47</sup> A German study has showed, however, that the positive effects of travel outweighed the health problems, and travel had a positive effect on subjectively perceived health status.<sup>53</sup> Prospective studies based on post-travel questionnaires and interviews do not record deaths that have occurred during travel.

***Studies based on travel insurance claims and data from assistance organizations***

In contrast to reports described above, studies based on travel insurance claims (Table 2a) have reported respiratory diseases to be the most common category of illness.<sup>83,84</sup> In one Polish study, 75% of the claims were because of illness, 25% because of injury.<sup>83</sup>

Although acquired for other purposes, data of emergency assistance organizations have been suggested as potentially valuable sources of information on events taking place during the actual travel.<sup>85</sup> Three studies are based on data of emergency assistance services of single major insurance companies in Switzerland, Australia, and Norway<sup>85–87</sup> (Table 2b). Assistance had been necessary because of illness in 69 to 76% of cases, and because of injury in 24 to 31% of cases.<sup>85,87</sup> These studies show nearly equal proportions of genders; 22 to 32% of their travellers with health problems were over age 60. In the Norwegian study, the proportion of cases with illness increased with age, whereas most injuries had occurred in those in the age group 15 to 29 years.<sup>87</sup> Traumas had accounted for 24 to 31% of the cases in these studies, with most of the fractures in the extremities.<sup>85,87</sup> The illness-to-accident ratio was higher in developing than in developed countries, mostly attributed to infectious and gastrointestinal illness.<sup>85,87</sup> Infections were the most common illnesses in the Norwegian<sup>87</sup> and Swiss<sup>85</sup> studies (20% vs. 26%), musculoskeletal symptoms (28%) in the Australian<sup>86</sup> report. Rate of hospitalization was higher than in the prospective studies, ranging from 12%<sup>86</sup> to 46%,<sup>87</sup> which suggests that these cases represent more serious health problems than did those in prospective studies.<sup>87</sup> Aeromedical evacuation was needed in 2.3 to 2.5%,<sup>86,87</sup> the proportion of deaths ranged from 0.2%<sup>86</sup> to 3.7%.<sup>87</sup>

**Table 2** Studies on health problems abroad based on insurance claims and data of assistance organizations

First author, country, publication year	N	Gender, male, %	Age >60 y, %	Illness, %	Injury, %	Hospitalized, %	Repatriated by air ambulance, %	Death, %	Diagnostic categories of illnesses <sup>a</sup>
<b>2a Studies based on travel insurance claims of single major insurance companies</b>									
Tomazunas, <sup>83</sup> Poland, 2000	3 200	NA	NA	75	25	NA	NA	1.0	of all cases: 22% respiratory, 11% gastrointestinal (including diarrhoea), 9% circulatory, 5% ear, 5% genitourinary, 2% infectious diseases
Leggat, <sup>84</sup> Australia, 2002	569	NA	NA	100	NA	NA	NA	0.4	of all cases: 20% respiratory, 17% musculoskeletal, 14% gastrointestinal, 13% ear, nose, and throat, 7% dental, 7% vascular, 5% dermatological, 5% genitourinary
<b>2b Studies based on data of emergency assistance services of single major insurance companies</b>									
Somer, <sup>85</sup> Switzerland, 2003	242	52	28	69	31	NA	NA	NA	of all cases: 26% infections, 8% cardiovascular, 7% gastrointestinal (including diarrhoea)
Leggat, <sup>86</sup> Australia, 2005	400	46	22	NA	NA	12	2.5	0.2	of illnesses: 28% musculoskeletal, 15% gastrointestinal, 14% dental, 12% respiratory, 8% ear, nose, and throat, 6% dermatological, 4% genitourinary, 3% cardiovascular, 3% obstetric
Lerdal, <sup>87</sup> Norway, 2007	1 787	55	32	76	24	46	2.4	3.7	of illnesses: 20% infections (including traveller's diarrhoea and pulmonary infections), 10% pulmonary

<sup>a</sup>comparisons between studies not fully reliable, since the diagnostic categories were not uniform

## INJURY DURING TRAVEL

Accidents or injuries have been reported by 0.5 to 7% of travellers in the prospective cohort studies.<sup>2,3,49–53</sup> Studies based on travel insurance claims or data of assistance organizations have reported these in 24 to 31%.<sup>83,85,87</sup> McInnes<sup>88</sup> reviewed 25 studies on injury during foreign travel. Several of the studies reported injury deaths to be more common among tourists than among local residents, and young men as the most likely victims of trauma.<sup>88</sup> Injury, defined as “an event that has an external cause and is potentially preventable,” has proved one of the main causes of death during travel (18–35%).<sup>88</sup> Pre-travel advice should thus include advice on traffic, safety, and prevention of injuries.<sup>89</sup>

## DEATH DURING TRAVEL

While infections are frequent among travellers, they only rarely cause serious or long-term consequences and have been reported as rare causes of death during travel.<sup>76,90–92</sup> Cardiovascular diseases and injuries are much less frequent, yet account for the majority travel-related deaths.<sup>76,90–92</sup> In most studies, age-specific cardiovascular mortality has not been higher in travellers than in the non-travelling population, whereas accidents have been the leading cause of excess mortality, especially among the young<sup>76,90,92,93</sup> and male<sup>91</sup>. Lunetta's<sup>92</sup> analysis of the causes of death of Finnish travellers abroad during 1969–2007 showed cardiovascular diseases to be the most common cause (44%), yet injury-death rates were more than three times as high as in Finland and represented 27% of all deaths abroad, with a peak among 20– to 30-year-olds. As in other reports,<sup>88</sup> the most common causes of unintentional injury deaths were traffic accidents (45%) and drowning (16%), followed by falls and poisoning; infections caused only 1.3% of deaths.<sup>92</sup>

### 2.1.3. FACTORS INFLUENCING THE RISK OF HEALTH PROBLEMS RELATED TO TRAVEL

#### FACTORS ASSOCIATED WITH THE TRIP

##### *Destination*

Studies have shown significant differences in travellers' morbidity between geographical regions. The study of GeoSentinel,<sup>68</sup> comprising 17 353 travellers returning ill from 1996 to 2004, has reported systemic febrile illness more frequently among those returning from sub-Saharan Africa or southeast Asia, acute diarrhoea more from south-central Asia, and skin problems more from the Caribbean or

Central or South America. Malaria has been one of the three most frequent causes of systemic febrile illness in every region, and the most common cause of fever in travellers to sub-Saharan Africa.<sup>68</sup> Other studies have shown rather similar results, findings depending on destinations.<sup>2–4,27,33–37,49,52,53,70,74,82,94</sup> A sentinel-surveillance study on European travellers returning ill<sup>4</sup> has reported travel within Europe also to be associated with health risks: 17% had a gastro-intestinal illness, 14% had a respiratory illness, and 8% had some dermatological condition. Disease patterns of eastern and western Europe differed; cases with gastroenteritis, potentially vaccine-preventable diseases, acute sexually transmitted diseases (STD), and tuberculosis were diagnosed more frequently among those visiting eastern than western Europe.<sup>4</sup>

### ***Duration of travel***

The longer a trip's duration, the higher the risk for developing illness.<sup>2,3,34,49,51–53</sup> In a study exploring journeys lasting less than three months, Hill has found the chance of becoming ill to increase by 3 to 4% with each travel day.<sup>2</sup> Long-term travellers and expatriates who reside abroad for years differ from other travellers with respect to exposures and risks. A GeoSentinel analysis has showed malaria, prolonged gastrointestinal symptoms and protozoal infections, eosinophilia, cutaneous leishmaniasis, schistosomiasis, and prolonged fatigue to be more frequent among long-term than short-term travellers.<sup>95</sup> An analysis of returning travellers has showed latent tuberculosis more frequently among expatriates than others; volunteer-worker expatriates presented more frequently with parasitic infections, business expatriates with vector-borne and vaccine-preventable infections.<sup>96</sup>

## **FACTORS ASSOCIATED WITH THE TRAVELLER**

### ***Sex and gender issues***

A GeoSentinel study<sup>97</sup> has shown women to obtain pre-travel advice more than men do, and to have after travel more frequently all types of diarrhoea, upper respiratory and urinary tract infections, psychological stressors, oral and dental conditions, and adverse reactions to medications. Men have been shown more likely to have febrile and vector-borne diseases such as malaria, leishmaniasis, and rickettsioses; sexually transmitted diseases; viral hepatitis; and non-infectious problems including cardiovascular disease. The authors concluded that some of the differences may be related to individuals' sex and some to gender-related behaviour.<sup>97</sup> Ill women have been less likely to be hospitalized on their return than men.<sup>27,97</sup> Studies on febrile hospitalized travellers after travel have also shown a male predominance.<sup>26,94,98–102</sup>

## **Age**

### *Children*

Studies on children, similar to those on adults, have shown an association between morbidity and geographical area visited,<sup>56,103–105</sup> and diarrhoea to be the most common post-travel health problem.<sup>103–105</sup> Traveller's diarrhoea has been more severe in children under 12 than in older age groups, and some studies have shown the highest rates among children aged <2 years.<sup>48,54,55</sup>

One Swiss study<sup>54</sup> has showed no difference in morbidity during travel between children and their adult relatives, with the exception of fever as being more frequent in children. By contrast, a Dutch study<sup>56</sup> has showed those in the age-group 12 to 18 years with higher morbidity than their parents; as a cause, the authors suggested that children of this age are no longer under the strict supervision of their parents, and may take health risks. Their most common health problems were mild skin problems and abdominal complaints.

Post-travel data of GeoSentinel<sup>103</sup> has showed in children a higher proportionate morbidity from gastroenteritis, respiratory disorders, and dermatological syndromes than in adults. Children have been more likely than adults to be visiting friends and relatives (VFR), not to have received pre-travel counselling, and to require hospitalization after travel. Their most common diagnoses have been diarrhoea (25%), systemic febrile illness (23%), and respiratory disorders (11%); the most common systemic febrile illness has been malaria (35%). No deaths occurred.<sup>103</sup> A post-travel study in one German university hospital<sup>104</sup> has showed 50% of patients in age group 0 to 4 years to be VFR. Another study in a similar setting in Switzerland<sup>105</sup> has reported a potentially serious illness in 4% of ill paediatric travellers, nearly all of them VFR. Children visiting friends and relatives are thus considered a vulnerable risk group of travellers.<sup>106</sup>

### *Young adults*

The rate of health problems is reportedly higher among young than older travellers.<sup>3,37,47,49,52,53,107–109</sup> Young adult travellers have also been described to experience subjectively health problems more often than those older, probably because of lack of experience in travel and in being ill.<sup>47</sup> Young adults, especially young men, are more prone to injury and accident-related death than are other travellers.<sup>88</sup>

## *The elderly*

A prospective study on travellers over age 60<sup>110</sup> showed them to comply with health recommendations more frequently than do those aged 20 to 30. Traveller's diarrhoea proved less common in the older age group (19% vs. 34%),<sup>110</sup> as shown also in other studies.<sup>109</sup> This finding may in part be explained by those older being more cautious and partly by intestinal immunity developing with repeated lifetime exposures.<sup>109</sup> A sentinel study comparing those over 60 to 18- to 45-year-olds<sup>111</sup> showed lower proportional morbidity in the older age group from acute diarrhoea and upper-respiratory-tract infections, malaria, and dengue; and higher morbidity from arthropod bites, rickettsiosis, severe malaria, lower-respiratory-tract infections, urinary tract infections, diseases of the upper gastrointestinal tract, phlebitis, pulmonary embolism, heart disease, trauma, and injury; the older age group had a higher death-rate.<sup>111</sup>

## **PURPOSE OF TRAVEL**

### ***VFR travellers***

A traveller visiting friends and relatives (VFR) has recently been re-defined as "a person whose primary purpose of travel is to visit friends or relatives and for whom there is a gradient of epidemiologic risk between home and destination, regardless of race, ethnicity, or administrative/legal status."<sup>112</sup> VFRs represent a distinct group of travellers at increased risk for travel-related health problems.<sup>113</sup> They stay in close contact with the local population, the trip often lasts longer, and they are more exposed to health risks than are other travellers.<sup>114</sup> VFR travellers less often seek pre-travel advice,<sup>41,114,115</sup> and are more likely than other travellers to be hospitalized and have serious illnesses after travel.<sup>114,115</sup> They have been more likely than other travellers to be diagnosed with malaria,<sup>70,74,79,100–102,114,116</sup> typhoid fever,<sup>115</sup> other systemic febrile illnesses,<sup>115</sup> respiratory infections,<sup>115</sup> influenza,<sup>117</sup> tuberculosis,<sup>115</sup> viral hepatitis,<sup>114</sup> HIV-infection,<sup>114</sup> sexually transmitted infections,<sup>114</sup> and intestinal parasitic infections;<sup>115</sup> yet less often with acute diarrhoea<sup>114,115</sup> or dermatologic conditions.<sup>115</sup> Malaria cases of VFR travellers have been mostly reported among those visiting sub-Saharan Africa.<sup>70,74,100,101,114</sup>

### ***Occupational travellers***

Studies on occupational travellers have shown higher rates of illness and injury and a higher frequency of psychological problems than in other types of travellers,<sup>118</sup> with the most common disease reported as being diarrhoea.<sup>118,119</sup> In a study on insurance claims of World Bank employees,<sup>120</sup> rates of infectious and intestinal diseases and diseases of the skin and subcutaneous tissue increased with number of international missions; the greatest excess morbidity related to travel was in psychological disorders.

## **2.1.4. TRAVELLERS' MOST COMMON DISEASES**

### **GASTROINTESTINAL INFECTIONS**

#### ***Traveller's diarrhoea***

The most common travel-associated disease is traveller's diarrhoea (TD), affecting 20 to 60% of those travelling from developed to developing countries<sup>107,121,122</sup> and estimated to affect annually at least 11 million individuals.<sup>123</sup> TD is defined by World Health Organization (WHO) criteria<sup>124</sup> as the passage of three or more loose or liquid stools per day, or more frequently than is normal for the individual. TD incidence depends on travel- and traveller-related risk factors.<sup>109</sup>

#### ***Travel-related risk factors of TD***

The most important travel-related risk factor is destination. Three risk areas have been defined according to TD incidence during a 2-week stay: low-risk areas with an incidence of 8% or less as including central and northern Europe, the USA, Canada, Australia, and New Zealand; intermediate-risk areas with an incidence of 8 to 20% comprising southern and eastern Europe, Russia, Japan, the Caribbean, Chile, Argentina, and South Africa; high-risk areas with an incidence of 20 to 90% including the Middle East, Asia, Central and South America, and Africa.<sup>107</sup> Risk varies between regions, countries, and even hotels.<sup>38,39,107</sup> A review by Steffen in 2005<sup>107</sup> showed a reduction in TD rates during recent decades in southern Europe, but not in other destinations. The second most often recognized travel-related factor is trip duration; risk is highest during the first week<sup>125</sup> and declines with duration of stay, probably because of acquired immunity to enteropathogens.<sup>21</sup> The third factor is type of travel: the risk increases the more adventurous the trip.<sup>126</sup>



### *Traveller-related risk factors of TD*

Travellers from countries with high sanitary standards have been shown to have higher TD rates than do travellers from less developed countries, suggesting lack of acquired intestinal immunity.<sup>125,127</sup> The risk for TD has appeared highest in infants, toddlers, and young adults,<sup>21,39,48</sup> and to be unrelated to gender.<sup>39,109</sup> Recognized predisposing risk factors for gastrointestinal infections include genetic susceptibility,<sup>107,121,123,128</sup> medications reducing gastric acidity,<sup>129,130</sup> and immunosuppression.<sup>131</sup>

### *Aetiology and clinical picture of TD*

Bacteria and their toxins have been reported to cause as many as 75% of the TD cases.<sup>132,133</sup> The causative micro-organism has remained unidentified in up to half the cases,<sup>132–135</sup> but new diagnostic methods may improve diagnostic accuracy.<sup>136–139</sup> The usual incubation period is 4 to 7 days, 90% of cases presenting during the first 2 weeks of the stay.<sup>109</sup> Half of such travellers are incapacitated for at least one day, 20% are confined to bed for 1 to 2 days. Medical consultation is needed in 5 to 15%, but need for hospitalization is rare. TD is usually self-limiting by 5 days without treatment, but may result in complications in those with underlying morbidity. Antimicrobials can shorten the illness by 1 to 2 days.<sup>109</sup> The effect of food hygienic measures in the prevention of TD has proved to be limited.<sup>39,140,141</sup>

### *Gastrointestinal symptoms after travel*

Studies of the GeoSentinel network on travellers returning ill have showed the highest risk for post-travel gastrointestinal problems to occur after journeys to South Asia, followed by sub-Saharan Africa and South America,<sup>80</sup> and post-travel symptoms to be more common in women.<sup>97,108</sup>

## **RESPIRATORY INFECTIONS**

Acute respiratory infections have occurred in 2 to 26% of travellers during<sup>2,3,33–37,49–53,81</sup> and in 8 to 11% following travel.<sup>4,68,70,74</sup> In the prospective study of Hill,<sup>2</sup> respiratory tract symptoms were reported by 26% during and by 10% following travel.

In a GeoSentinel study on returned travellers,<sup>117</sup> 8% of all infections were of the respiratory tract, among which, the most common diagnosis were nonspecific upper respiratory infection (47%), followed by pharyngitis (13%). Lower-respiratory-tract infections accounted for 40%: bronchitis for 20%, pneumonia for 14%, and

influenza for 6%. Lower-respiratory-tract infections have been associated with male gender and increasing age, with risk for upper-respiratory-tract infection greater in younger persons. Influenza has been associated with travel visiting friends and relatives and trips of long duration, but not with traveller's age.<sup>117</sup>

Mutsch and colleagues<sup>142</sup> have demonstrated seroconversion of influenza-specific antibodies in 2.8% of 1 450 travellers and calculated an incidence of 1.0 influenza-associated events per 1 000 person-months abroad, suggesting influenza as the most frequent vaccine-preventable infection of travellers to subtropical and tropical countries. During the A(H1N1) influenza pandemic in 2009, other influenza viruses and rhinovirus were also frequent causes of respiratory infection in travellers.<sup>143</sup>

### 2.1.5. ILLNESS AFTER TRAVEL

Few studies exist on overall travel-related illness or mortality after travel, and none on long-term morbidity.

Prospective studies on health problems during travel have followed travellers for up to 7 months; 25 to 33% of these travellers have been ill on or after return,<sup>2,3,47</sup> 9 to 46% have consulted a physician,<sup>2,47,50,51</sup> and 0.1 to 1% have been hospitalized.<sup>47,50</sup> In one Norwegian study,<sup>47</sup> 25% had health problems after the trip, 9% had consulted a doctor, and 1% had been hospitalized; 50% had suffered gastrointestinal problems, 25% upper-respiratory infections, 18% had experienced general ill health, and 8% skin problems. In the Hill study,<sup>2</sup> 46% of ill travellers sought medical care after travel, compared to 12% during travel; the most common post-travel problems were gastrointestinal symptoms (31%), followed by respiratory tract illness (24%), febrile episodes (13%), and skin problems (11%).

A US study examining causes of travel-related deaths after return has found most to be cardiovascular (70%).<sup>144</sup> The proportion of infections was found higher than in studies on death during travel<sup>91,92</sup> (12% vs. 1.3–3%). Pneumonia was the most common infectious cause of death (53%); 73% of these patients had some underlying chronic condition.<sup>144</sup>

### INFECTIONS IN RETURNED TRAVELLERS

Most studies on epidemiology of illness in returned travellers are based on data from either a single referral centre<sup>24,25,27,94,100,114,145</sup> or from a surveillance network of centres for tropical and travel medicine,<sup>4,68,70,74</sup> and they mainly describe infections (Table 3).

Studies based on hospital data have reported fever as the most common presenting symptom (43–77%).<sup>27,100,114,145</sup> Of the final diagnoses, gastrointestinal diseases have represented 9 to 49%, respiratory diseases 3 to 12%, and skin diseases 5 to 8%.<sup>24,25,27,94,100,114,145</sup> Malaria has been the most common single diagnosis in hospitalized patients (9–49%).<sup>24,25,27,94,100,145</sup> In studies reporting mortality data, the figures have proved to be low (0.2–0.6%).<sup>94,114</sup>

In studies based on data of surveillance centres,<sup>4,68,70,74</sup> including mainly outpatients, the most common diagnostic categories have been gastrointestinal infections (33–42%), systemic febrile illnesses without localizing symptoms (20–23%), and skin diseases (12–20%). Malaria has been the most common single diagnosis, followed by dengue. Malaria diagnoses have been proportionately most frequent in those returning from Africa.

## FEVER IN RETURNED TRAVELLERS

Several studies have presented fever as one of the most common reasons (28–77%) for seeking medical help after travel.<sup>27,100,114,145,147</sup> When examining travellers with fever without focal symptoms, the clinician faces a multitude of diagnostic alternatives.<sup>148</sup> The most important task is to recognize the treatable potentially life-threatening diseases<sup>148,149</sup> and the few infections highly transmissible from person to person requiring special infection-control measures.<sup>148</sup> When examining a febrile returned traveller, it is essential to take a chronological history covering travel itinerary and course of illness. This information, combined with knowledge of infection-specific incubation periods, allows the clinician to exclude diagnoses which are, time-wise, unlikely and to focus on the more likely diagnoses.<sup>148</sup>

Data on fever in returned travellers have been based on studies conducted in tertiary hospitals or referral centres for travel or tropical medicine.<sup>26,27,94,98–102,147</sup> Outpatients were included in one single-centre study<sup>101</sup> (73%) and one multicentre study<sup>147</sup> (74%); other papers have described inpatients only. Thus they all represent selected patient material. Median age of the patients has been 30 to 38 years, the majority of them (59–71%) male. The proportion of VFR travellers has ranged from 0 to 59%, which may affect the findings of individual studies. The region most commonly visited has been sub-Saharan Africa (34–86%), except for the Australian studies,<sup>26,94</sup> in which the most common location has been Asia and the Pacific. The results of these studies are presented in Table 4 and discussed below.

**Table 3** Studies on illness after travel

First author, country, publication year	Study population	Method of data collection	N	VFR or immigrants, %	Gastrointestinal disease, %	Respiratory disease, %	Skin disease, %	Systemic febrile illness, %
<b>Studies based on data from a single centre</b>								
McKendrick, <sup>25</sup> UK, 2003	returning travellers admitted to one hospital	retrospective review of discharge diagnoses	2 202	NA	36	13	5	NA
Roberts, <sup>24</sup> UK, 2003	all imported infections on the infectious diseases ward of one regional infectious diseases referral hospital	retrospective review of patient records	301	NA	9	6	7	NA
Ansart, <sup>100</sup> France, 2005	all patients >15 years old with travel-associated health complaints in tropical diseases unit of one hospital	prospective study	622	34	19	12	23 <sup>a</sup>	NA
Stienlauf, <sup>27</sup> Israel, 2005	all causes of post-travel hospitalization in a major tertiary care hospital	retrospective review of patient records	211	8	11	0	5	NA
O'Brien, <sup>94</sup> Australia, 2006	all adult travellers with an illness likely to be acquired overseas in two hospital-based infectious diseases units	prospective study	917	0	15	3	5	NA
Fenner, <sup>114</sup> Switzerland 2007	patients seeking treatment for travel-associated illness in tertiary hospital; 80% outpatients -travellers -VFR	part of GeoSentinel surveillance data collection	217 121	0 100	26 12	13 12	7 5	NA NA
Leroy, <sup>145</sup> France, 2008	patients >16 years old hospitalized in one infectious diseases department for presumed travel-related illness	retrospective review of patient records	230	10	49	15	8	NA

First author, country, publication year	Study population	Method of data collection	N	VFR or immigrants, %	Gastrointestinal disease, %	Respiratory disease, %	Skin disease, %	Systemic febrile illness, %
<b>Multicentre studies</b>								
Freedman, <sup>68</sup> worldwide multicentre study, 2006	ill travellers returned from developing countries who sought medical advice from GeoSentinel sites for a presumed travel-related illness	clinician-based sentinel surveillance data from 30 specialized travel or tropical medicine clinics	17 353	15	42	8	17	23
Gautret, <sup>70</sup> European multicentre study, 2009	ill western European returned travellers who sought medical help from European GeoSentinel sites	clinician-based sentinel surveillance data from specialized travel clinics or tropical medicine clinics	17 228	14	40	10	20	20
Field, <sup>4</sup> European multicentre study, 2010	ill returned European travellers who sought medical help from EuroTravNet core sites	clinician-based sentinel surveillance data from 13 specialized travel or tropical medicine clinics	6 957	21	33	8	12	20
Leder, <sup>74</sup> worldwide multicentre study, 2013	ill travellers returned both from developed and developing countries who sought medical advice from a GeoSentinel site and diagnosed with a travel-related disease	clinician-based sentinel surveillance data from 53 specialized travel clinics or tropical medicine clinics	42 173	16	34	11	20	23

<sup>a</sup>centre specialised in tropical dermatology

VFR = visiting friends and relatives

**Table 4** Studies on fever after travel

First author, country, publication year	Number of febrile patients	VFR, %	Destination sub-Saharan Africa, %	Reason for fever								Death, %			
				Gastro intestinal disease, %	Respiratory infection, %	Skin infection, %	Malaria, %	Sepsis, %	Dengue, %	Influenza, %	HIV, %		Non specific viral infection, %	Non infectious cause of fever, %	Unknown, %
Doherty, <sup>98</sup> UK, 1995	195	NA	60	6	4	1	42	2	6	0	1	25	0	0	NA
O'Brien, <sup>26</sup> Australia, 2001	232	0	15	14	24	3	27	0.4	8	5	0.4	0	2	9	NA
Antinori, <sup>99</sup> Italy, 2004	147	27	61	5	3	0	48	0.7	3	0	0.7	12	5	0	NA
Ansart, <sup>100</sup> France, 2005	272	34 <sup>a</sup>	58 <sup>a</sup>	23	16	12	21	NA	6	NA	0.8	4	0	5	NA
Stienlauf, <sup>27</sup> Israel, 2005	166	8 <sup>a</sup>	34 <sup>a</sup>	7	3	3	26	NA	13	NA	NA	NA	0	16	NA
Bottieu, <sup>101</sup> Belgium, 2006	1 743	14	68	6	11	4	29	0.1	3	NA	1.5	NA	2	24	0.5
O'Brien, <sup>94</sup> Australia, 2006	624	0	15 <sup>a</sup>	12	16	2	27	NA	7	4	NA	4	NA	7	0.2
Parola, <sup>102</sup> France, 2006	613	59	86	4	4	0.2	75	NA	2	0	0.3	NA	0.7	11	NA
Wilson, <sup>147</sup> multicentre study, 2007	6 957	21	37	15	14	4	21	NA	6	1	NA	NA	NA	22	0.2

<sup>a</sup>of all ill returned travellers  
VFR = visiting friends and relatives

### ***Causes of fever in returned travellers***

Malaria has been reported as the most common single reason for travel-related fever without local findings (21–75%),<sup>26,27,94,98–102,147</sup> and the most common tropical disease causing death.<sup>101,147</sup> Two of the studies have reported tropical diseases to account for 36%<sup>100</sup> and 39%<sup>101</sup> of the febrile diseases. In addition to tropical diseases are worldwide infections.<sup>26,94,98,100,101,147</sup> Six studies have reported newly diagnosed HIV infections in 0.3 to 1.5% of patients, yet not all febrile returned travellers were tested for HIV.<sup>26,98–102</sup> In a minority of cases (0–5%), the cause of fever has been non-infectious.<sup>26,99,101,102</sup> Three studies have reported 10 to 16% of patients as with more than one diagnosis.<sup>98,99,101</sup> Reported mortality has been 0.2 to 0.5%.<sup>94,101,147</sup>

The proportion of those remaining without a confirmed diagnosis has ranged in various studies from 5 to 24%.<sup>26,27,94,100–102,147</sup> In febrile returned travellers whose diagnosis had remained unknown in routine investigations, a Swedish study, using paired sera, established a diagnosis in 21%. The most common diagnosis revealed was influenza (10%), followed by rickettsial infection (5%), dengue (3%), leptospirosis (2%), and Q-fever (1%).<sup>150</sup> Influenza has been diagnosed as the cause of fever after travel in 0 to 5% in other studies.<sup>26,94,98,99,102,147</sup> These data suggest that influenza in travellers is underdiagnosed.<sup>150</sup>

A GeoSentinel study has showed patients with fever to be hospitalized more often than are those without fever (26% vs. 3%)<sup>68</sup>; of the febrile patients, 35% have been diagnosed with a febrile systemic illness, 15% with febrile diarrhoeal disease, and 14% with respiratory infection.<sup>147</sup> After malaria, the most common single systemic febrile illnesses in the GeoSentinel study have been dengue, enteric fever, and rickettsioses.<sup>147</sup> In the Belgian study,<sup>101</sup> the most frequently diagnosed tropical infections after malaria have been rickettsial infections and dengue.

### ***Travel destination and cause of fever***

Fever aetiology depends on travel destination. *P. falciparum* malaria has been the most common cause of fever in travellers returning from sub-Saharan Africa,<sup>26,27,68,94,99–102,147</sup> whereas dengue, malaria, and enteric fever have been among the three most common causes in travellers to Asia,<sup>68,101</sup> and dengue the most frequent cause in those visiting the Americas.<sup>68,101</sup> Rickettsiosis<sup>68,101</sup> and acute schistosomiasis<sup>101</sup> have affected almost exclusively travellers to sub-Saharan Africa.

***Purpose of travel and cause of fever***

VFR travellers have represented 8 to 59% of ill febrile returned travellers.<sup>27,99–102,147</sup> In most studies, the majority of diagnosed malaria cases have been in VFRs, most of them *Plasmodium falciparum* infections among those visiting sub-Saharan Africa.<sup>100–102,147</sup>

***Factors predictive for malaria in febrile returned travellers***

Several studies have sought factors predicting malaria as the cause of travel-related fever. Features associated with malaria have been fever without localizing symptoms,<sup>151</sup> enlarged spleen,<sup>151</sup> thrombocytopenia,<sup>151–153</sup> leukocytopenia,<sup>153</sup> elevated lactate dehydrogenase,<sup>153</sup> and hyperbilirubinemia.<sup>151,153</sup> No clinical or biological parameter has proved, however, to have both good specificity and sensitivity to differentiate malaria from other diseases.<sup>146,154</sup>

In conclusion, malaria should be suspected in all febrile travellers returning from malaria-endemic areas and should be excluded by laboratory tests.<sup>146,154</sup>

**2.2. MALARIA****2.2.1. GLOBAL EPIDEMIOLOGY OF MALARIA**

Nearly half the world's population is at risk for malaria. In 2013, malaria was endemic in 104 countries or territories in tropical and temperate regions.<sup>155,156</sup> The WHO estimated that over 200 million cases and 627 000 malaria-related deaths occurred globally in 2012<sup>155</sup>; mortality may, however, be underestimated.<sup>157</sup> Most cases (80%) and most deaths (90%) occurred in sub-Saharan Africa, and most deaths (77%) were in children under age 5.<sup>155</sup>

Malaria is caused by protozoan parasites of the genus *Plasmodium*. Five species can infect humans: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and the zoonotic species *P. knowlesi*. Of these, *P. falciparum* is the most common; it predominates in Africa and causes most of the malaria-related deaths. *P. vivax* is more widespread, but less serious; the other species are found much less frequently.<sup>155</sup> *P. vivax* is widely distributed, because it is able to develop in the mosquito vector at lower temperatures and to survive at higher altitudes and in cooler climates than *P. falciparum* can. It also has a dormant liver stage (hypnozoite) enabling it to survive during periods when no mosquitoes are present. Many African populations have a high frequency of Duffy negativity, which makes red blood cells resistant to *P. vivax* infection; this species is more rare in Africa than in other areas.<sup>155</sup>



Transmission intensity depends on factors related to the parasite, the vector, the human host, and the environment. Malaria is transmitted through the bites of *Anopheles* mosquitoes, which breed in water. Only about 30 of the more than 400 *Anopheles* species are effective vectors, these all bite at night. The African vector species has a long lifespan and prefers to bite humans rather than animals, the main reasons why transmission in Africa is high.<sup>155</sup> In most of Asia and South and Central America, transmission is mainly low and seasonal, and prevalences of *P. falciparum* and *P. vivax* malaria are approximately equal. In these areas, most people receive one or fewer infectious bites per year, whereas in most of sub-Saharan Africa, where *P. falciparum* predominates, and in parts of Oceania, transmission intensities in some areas are as high as 1 000 bites per year.<sup>158</sup>

Since 2000, malaria control programmes have led to a reduction in malaria incidence and mortality. Between 2000 and 2012, estimated malaria mortality rates fell worldwide by 45% in all age groups, and by 51% in children under 5. Malaria continues, however, to be a major public-health problem in endemic areas, especially in sub-Saharan Africa.<sup>155</sup>

## 2.2.2. TRANSMISSION, PATHOGENESIS, AND CLINICAL PICTURE OF MALARIA

Human malaria infection is transmitted from person to person by the bite of an infected female *Anopheles* mosquito; transmission is also possible via blood and by congenital transmission. Within a few minutes, through the bloodstream, *Plasmodium* sporozoites enter the liver, where they invade hepatocytes and multiply asexually into tissue schizonts. *P. vivax* and *P. ovale* may remain in the liver as dormant hypnozoites for several months, even years, before proceeding to their next stage. In *P. falciparum* infection, the liver schizonts rupture after 1 to 2 weeks, in other *Plasmodium* species after a longer period. Rupturing schizonts release into the bloodstream merozoites, which invade red blood cells of various ages (erythrocytic stage). Within red blood cells, the merozoites mature successively from ring forms to trophozoites and further to mature red cell schizonts over a period of 24 hours (*P. knowlesi*), 48 hours (*P. vivax*, *P. ovale*, *P. falciparum*), or 72 hours (*P. malariae*). Clinical symptoms appear when the blood cells rupture, releasing new daughter merozoites and pro-inflammatory cytokines. Most released merozoites continue the asexual circle, infecting new red cells; a few differentiate into male or female gametocytes (sexual forms) which may be ingested by a mosquito along with a blood meal. The sexual cycle, formation of new sporozoites, takes place in the mosquito, completing the life cycle.<sup>158</sup>

*P. falciparum* and *P. knowlesi* can infect all stages of red blood cells; parasitaemia (proportion of infected red cells) above 2% is associated with risk of

complications and death.<sup>158</sup> *P. vivax*, *P. ovale*, and *P. malariae* invade red blood cells selectively (e.g. *P. vivax* only young erythrocytes), and parasitaemia is usually less than 1%.<sup>158</sup> *P. falciparum* infection causes sequestration of infected red cells and their adherence to uninfected cells within the small vessels, leading to obstruction of blood flow, breakdown of the endothelial barrier, inflammation, and a complex cytokine reaction and host response.<sup>158</sup> These events may result in tissue anoxia, multi-organ failure, and death.<sup>158</sup> Other *Plasmodium* species are not sequestered substantially,<sup>158</sup> and usually have a benign course. Recent studies have, however, reported from Indonesian Papua and India complicated *P. vivax* infections with mortality (0.8–3.9%).<sup>159–165</sup> The pathogenesis of complicated *P. vivax* infection and that of *P. knowlesi* infection remain to be explored.

In *P. falciparum* malaria, the incubation period from transmission to symptoms is at least 7 days; in approximately 95% of cases symptoms occur within 4 weeks. In *P. knowlesi* malaria, the incubation period is 9 to 12 days. In other species, symptoms may appear in 12 days to several months, in *P. vivax* and *P. ovale* even years after initial infection.<sup>158,166</sup> The dominant symptoms of malaria in those who are non-immune are high fever with chills, often combined with headache and myalgias, sometimes with nausea, diarrhoea, or cough.<sup>167</sup> Bouts of fever typically appear at regular intervals in *P. vivax* (48 h), *P. ovale* (48 h), and *P. malariae* (72 h) infections. In *P. falciparum* infection, fever exhibits no regular pattern. Clinically, infection caused by *P. knowlesi* is similar to that of *P. falciparum*.<sup>168–173</sup>

Frequent infections in highly endemic areas result in development of partial immunity to clinical episodes of malaria.<sup>158</sup> Asymptomatic, persistent *P. falciparum* parasitemia has been seen in immigrants even years after their leaving the endemic area.<sup>174–178</sup> Degree of protective immunity is proportional to transmission intensity and requires repeated encounters with the parasite antigen<sup>158</sup>; it is therefore gradually lost after the individual leaves the endemic area. At highest risk for symptomatic and severe malaria are individuals without any immunity, like small children and non-immune visitors in malaria-endemic areas. Pregnant women<sup>179</sup> and those who are immunosuppressed<sup>180</sup> are also more prone to complications than are others.

### 2.2.3. MALARIA IN TRAVELLERS

#### RISK FOR MALARIA IN TRAVELLERS

The number of malaria cases in travellers from industrialized countries has been estimated to be 25 000/year; of these, approximately 10 000 are reported, and 150 are fatal.<sup>181</sup> The risk for acquiring malaria of non-immune travellers to malaria-endemic countries has been calculated at 1 to 357/100 000, depending on country.<sup>61</sup>

Risk is highest in sub-Saharan Africa and Oceania, intermediate in southern Asia, and lowest in Central America, South America, and southeast Asia.<sup>61,79</sup> Within sub-Saharan Africa, risk is highest in western Africa.<sup>180,182</sup> The extent of transmission varies widely and may be focal within countries and areas. Risk increases with length of stay; long-term travellers<sup>95</sup> and VFR travellers<sup>72,74,79,100–102,114,116</sup> are at highest risk.

## SEVERE MALARIA AND MORTALITY IN TRAVELLERS

The case fatality rate of imported *Plasmodium falciparum* malaria has ranged in most reports between 0.4% and 3.8%.<sup>65,183–190</sup> Risk for severe malaria and death is related to several factors: delay between onset of symptoms and start of proper treatment,<sup>183,185,189,191–193</sup> increasing age in the elderly,<sup>183,184,186,187,189,192,194–196</sup> and failure to take antimalarial chemoprophylaxis.<sup>183–187,189,191,192,194</sup> These studies suggest that even when chemoprophylaxis has failed to prevent malaria, it still has significantly reduced risk of death.

## PREVENTION OF MALARIA IN TRAVELLERS

Risk for malaria can be reduced by preventing mosquito bites between dusk and dawn by means of clothing, insect repellents, and bed nets, and by use of appropriate chemoprophylaxis.<sup>180,182,197–200</sup> The WHO<sup>201</sup> and various national malaria chemoprophylaxis guidelines<sup>122,202–205</sup> uniformly recommend continuous chemoprophylaxis for travellers to high-risk areas. In contrast, recommendations regarding areas with low-to-moderate malaria risk, or regions with *P. vivax* predominating, vary among national guidelines<sup>122,202–205</sup> and vary by expert opinion<sup>206–209</sup> depending on the risk-benefit analysis applied. Some authorities recommend continuous chemoprophylaxis, others seasonal chemoprophylaxis, no chemoprophylaxis, or standby emergency self-treatment.<sup>210</sup>

The primary goal of malaria chemoprophylaxis is prevention of death, mainly caused by *P. falciparum*; the secondary goal is to prevent clinical malaria.<sup>199,210</sup> The current recommended first-line drugs (atovaquone-proguanil, doxycycline, and mefloquine) are all considered over 90% effective in preventing clinical episodes of primary malaria infection.<sup>180,199</sup>

Chloroquine is effective against *P. falciparum* only in Central America west of the Panama Canal, in the Caribbean, and in the Middle East. Mefloquine resistance has developed on the eastern and western borders of Thailand and in adjacent countries. Chloroquine-resistant *P. vivax* exists in Papua New Guinea and Indonesia.<sup>180,199</sup>

Atovaquone-proguanil, chloroquine, doxycycline, and mefloquine are active against the blood-stage parasites, but do not prevent relapsing infections caused by *P. vivax* and *P. ovale* hypnozoites. Primaquine is the only drug acting on liver hypnozoites and is used for completing the treatment of *P. vivax* and *P. ovale* malaria. Primaquine is also an alternative chemoprophylaxis for individuals not tolerating other drugs, provided that glucose-6-phosphate dehydrogenase (G6PD) deficiency has been excluded.<sup>180,182,197,199,210</sup>

A randomized trial of adverse events related to prophylactic antimalarial drug regimens in non-immune travellers<sup>211</sup> has showed atovaquone-proguanil and doxycycline to be better tolerated than are mefloquine and a combination of chloroquine and proguanil. A Cochrane review<sup>212</sup> has shown the rate of adverse events to be equal for atovaquone-proguanil and doxycycline, slightly higher for mefloquine, and highest for a combination of chloroquine and proguanil.

Studies of travellers' knowledge, attitudes, and practices toward malaria prevention have shown gaps and need for improvement.<sup>40–45,213–215</sup> While chemoprophylaxis clearly reduces the risk for acquiring malaria in non-immune persons, noncompliance with prophylactic medication has repeatedly been identified as a major factor raising risk for imported malaria.<sup>49,57,214,216–222</sup> A study comparing self-reported compliance with antimalarial prophylaxis and blood concentrations of antimalarial drugs has shown that travellers significantly overestimate their own compliance.<sup>223</sup>

## DIAGNOSIS OF MALARIA

Symptoms of malaria are non-specific and cannot be clinically distinguished from those of other febrile diseases.<sup>146,154</sup> The gold standard of malaria diagnostics is light microscopy of Giemsa-stained thin and thick blood smears, but this requires expertise and time. Polymerase chain reaction (PCR) tests are slightly more sensitive than microscopy and most useful for species identification and detection of mixed infections.<sup>224</sup> PCR tests are not helpful for acute diagnostics, because results are usually not available as quickly as microscopy.<sup>122</sup> Rapid diagnostic tests (RDTs) are increasingly used, especially outside specialized centres. RDTs have limitations and, in addition to them, microscopy is still necessary to determine species and parasitemia percentages. Parasitemia is an essential parameter in *P. falciparum* and *P. knowlesi* malaria for evaluation of whether the patient has complicated malaria and also for monitoring the effect of treatment.<sup>167,224</sup>

## TREATMENT OF MALARIA

WHO recommends oral artemisinin-based combination therapy (ACT) for uncomplicated *P. falciparum* malaria.<sup>225</sup> *P. vivax* malaria can be treated with chloroquine, except in areas where *P. vivax* resistance to chloroquine has been documented (Papua New Guinea and Indonesia). Severe malaria is treated with injectable artesunate, followed by a complete course of an effective oral ACT as soon as the patient can take oral medications.<sup>225,226</sup>

In non-endemic regions, treatment of malaria has varied between countries and centres; a retrospective analysis from 16 centres in 5 European countries, 2003–2009, showed 18 combination regimens for malaria treatment.<sup>227</sup> European experts published in 2012 recommendations for treatment of malaria in Europe,<sup>167</sup> ones which are in line with WHO guidelines. Oral ACTs are the recommended treatment of uncomplicated *P. falciparum* malaria, with atovaquone-proguanil as an alternative. If these first-line antimalarials are unavailable or cannot be used, a combination of quinine with either doxycycline or clindamycin, or mefloquine alone is the recommended second line treatment.<sup>167</sup> In treatment of complicated *P. falciparum* malaria, intravenous artesunate has proved superior to intravenous quinine as regards overall survival, and it is simpler and safer to administer.<sup>228,229</sup> Artesunate is the first-line treatment in complicated malaria<sup>167,226,230,231</sup>; intravenous quinine combined with doxycycline or clindamycin remains an alternative, if artesunate is unavailable or cannot be used.<sup>167</sup> Patients treated with intravenous artesunate should be monitored for possible haemolysis for 4 weeks after treatment.<sup>167,232–235</sup> ACTs are effective also against *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*, yet these species can be treated with chloroquine as well. After treatment of the acute infection, a course of primaquine is necessary in *P. vivax* and *P. ovale* malaria to prevent relapses from liver hypnozoites.<sup>167</sup>

### 2.2.4. IMPORTED MALARIA IN EUROPE

Earlier, malaria was endemic in Europe.<sup>236</sup> The last indigenous case in Finland was reported in 1954,<sup>237</sup> and in Italy in 1979.<sup>236</sup> Reintroduction of the disease to the continent remains possible.<sup>236</sup> The annual number of notified imported cases in European countries has been 10 000 to 13 000 (2–3/100 000 population) during more recent decades, with France, the UK, Germany, and Italy accounting for more than 70% of all cases.<sup>238,239</sup> In 2012, the WHO reported 5 500 cases of imported malaria in Europe,<sup>240</sup> yet this figure may be an underestimation.<sup>167</sup> Malaria is a notifiable disease in most European countries, but under-reporting may exist.<sup>167,236,238,241</sup> Mortality in imported *P. falciparum* malaria in Europe has in various studies ranged from none to 3%.<sup>184,186,187,189,190,192</sup>

Imported malaria in Europe has been diagnosed among native Europeans, VFR travellers, foreign visitors, and immigrants arriving from malaria-endemic areas. Various studies have reported data on cases of imported malaria from European hospitals,<sup>242–244</sup> cities,<sup>245,246</sup> areas,<sup>241,247</sup> or countries<sup>188,248,249</sup> (Table 5). Most of the imported cases in Europe have been *P. falciparum* infections acquired in sub-Saharan Africa,<sup>4,65,99–102,188,192,241–249</sup> similar to data in studies including non-European countries.<sup>68,74,79,147</sup> A large proportion (28–65%) of malaria patients diagnosed in Europe have been VFR travellers.<sup>188,241–249</sup> Regions for acquiring the infection reflect the geographic origin of the immigrant population in each European country and the risk for malaria in those regions. In most reports the majority of cases (52–98%) have been acquired in western Africa.<sup>188,241,243,244,247,248</sup> An analysis of seven European studies in 2003 showed that 43% of imported malaria cases had been diagnosed in foreign-born residents, most of them VFR travellers, and their proportion seemed to be increasing.<sup>116</sup> Many later studies have confirmed the increase in proportion of VFR travellers among malaria patients.<sup>188,243,246–248</sup> In the UK, during 1987–2006, the number of reported malaria cases increased steadily, attributable to *P. falciparum* cases in VFR travellers to western Africa. During the same 20-year period, a decrease occurred in the number of *P. vivax* cases in travellers to southern Asia, most of them VFRs,<sup>248</sup> which accords with other findings of declining malaria incidence in travellers to India.<sup>250</sup> In Italy, during 2000–2006, a constant decrease occurred in total incidence of imported malaria due to decrease in cases in travellers of Italian origin, while a concomitant increase was noted in the proportion of VFR travellers.<sup>188</sup> In contrast, in the Netherlands in 2000 to 2007, a decrease in incidence occurred both in tourists and in VFR travellers.<sup>249</sup>

**Table 5** Studies on imported malaria in Europe

First author, publication year	Region of collection of study material, country	Study period	Method	N	Plasmodium species		Region		Immigrants		Case fatality rate, %
					<i>P. falciparum</i> , %	<i>P. vivax</i> , %	sub-Saharan Africa, %	Asia, %	VFR, %	Recently arrived immigrants, %	
	<b>Hospital</b>										
Baas, <sup>242</sup> 2006	Amsterdam, Netherlands	2000–2002	prospective	302	82	9	86	7	57	9	0
Thierfelder, <sup>243</sup> 2008	Basel, Switzerland	1994–2004	retrospective	109	88	9	82	5	37	15	0
Rey, <sup>244</sup> 2010	Madrid, Spain	2005–2008	retrospective	57	95	0	98	2	62	29	0
	<b>City</b>										
Mascarello, <sup>245</sup> 2008	Verona, Italy	2000–2004	retrospective	380	77	5	95	5	41	13	NA
Millet, <sup>246</sup> 2008	Barcelona, Spain	1989–2005	prospective	1 579	71	NA	82	NA	41	14	3.9
	<b>Area</b>										
Espinosa-Vega, <sup>247</sup> 2011	Gran Canaria, Spain	1993–2006	retrospective	170	84	12	95	3	28	12	3.8
Unger, <sup>241</sup> 2011	Scotland, UK	2006–2008	retrospective	252	69	16	82	14	33	7	NA
	<b>National data</b>										
Smith, <sup>248</sup> 2008	UK	1987–2006	national notification data	39 300	63	28	72	26	65	9	0.5
Romi, <sup>88</sup> 2010	Italy	2000–2006	national notification data	5 219	83	16	93	5	57	NA	0.4
van Rijkevorsel, <sup>249</sup> 2010	Netherlands	2000–2007	national notification data	2 847	75	15	82	12	53	NA	NA

VFR = visiting friends and relatives

### 3 AIMS OF THE STUDY

This thesis investigated illness and injury in Finnish travellers, with a focus on infections. The main aim was to find tools for risk assessment, for pre-travel advice, and for post-travel examination of travellers.

#### SPECIFIC AIMS WERE:

1. to provide a comprehensive overview of illness and injury of Finnish travellers diagnosed while abroad, and to calculate the incidences in various geographic regions and countries (I)
2. to define the causes of fever in returning travellers and to improve clinical differential diagnostics (II)
3. to identify risk groups for imported malaria in Finland (III)
4. to analyze in detail the risk groups for imported malaria in Finland, and to explore whether *Plasmodium falciparum* infection can be contracted despite appropriate chemoprophylaxis (IV)



## 4 MATERIALS AND METHODS

### 4.1. STUDY I: ILLNESS AND INJURY OF FINNISH TRAVELLERS ABROAD

#### 4.1.1. MATERIAL

The study material comprised all Finnish travellers experiencing health problems abroad during 2010–2012, as recorded in the database of an assistance organization of insurance companies (SOS International). SOS covers approximately 95% of all Finnish cases abroad (77% of inpatient and 99.8% of outpatient cases) that are handled by assistance organizations. After a detailed analysis, these data were compared to the numbers of Finnish travellers in 2010 to 2012 as retrieved from the database of the Official Statistics of Finland (OSF).

#### 4.1.2. DATA COLLECTION

Methods and definitions are described in more detail in the original article.

#### *Data from the assistance organization*

All data are registered and handled in a computerized database. The following information was available for the study: age, gender, time and country of illness or injury, inpatient or outpatient status, main diagnosis, repatriation, and death. A coordinating doctor is assigned to 86% of the inpatient cases, and to 1% of outpatient cases; such doctors coded diagnoses according to the International Statistical Classification of Diseases and Related Health Problems (ICD–10). Uncomplicated inpatient cases and 99% of outpatient cases are handled by non-medical assistance coordinators; they recorded the diagnoses provided by clinicians abroad as open text. A single coordinating doctor (H.S.) later encoded these diagnoses (45 475 cases) according to the ICD–10 classification. Diagnostic categories were those of ICD–10 with the exception of infections, which were all separated from the organ-specific ICD–10 classification into a category of their own.

***Data on Finnish travellers***

The OSF data included annual numbers and average duration of at-least-overnight leisure and business trips abroad, and age-groups of travellers by region and country. Country-specific data were available for countries with >50 000 Finnish travellers/year. OSF data had initially been retrieved by monthly sample-based computer-assisted telephone interview surveys of the population of Finnish residents aged 15 to 74; the upper age limit was extended to 84 years in 2012. The samples had been drawn by systematic sampling from the central population register. In 2010 and 2011, the sample size had been 2 200 and, in 2012, 2 350 individuals per month.

***Calculation of incidence***

To be compatible with the OSF population, only adult cases aged 15 to 74 during 2010–2011 and 15 to 84 during 2012 were included, and the geographic classification of OSF was applied for the calculation of incidence. The incidence of illness or injury was calculated per 100 000 travel days in various geographical regions and countries.

**4.1.3. STATISTICAL ANALYSIS**

The descriptive statistics were analyzed with Microsoft Excel 2010 and IBM SPSS statistics 19.0. Differences between groups were tested with the chi-square test, student's t-test, and Mann-Whitney U-test, as appropriate. Risk factors for hospitalization were analyzed by logistic regression. Variables with  $p < 0.2$  in univariable analysis were subjected to a multivariable model. For variables lacking any reference category, deviation from average effect was used.

Credible intervals (95%CI) for travel days of travellers with insurance, and thus 95%CI for incidences, were estimated using Bayesian modeling with MCMC Gibbs sampling with informative priors. Following assumptions were used: proportion of travellers with insurance was lower (55–70%) for eastern and western Europe and higher (75–85%) for more distant destinations; trip durations were distributed similarly in 2010–2011 and in 2012. In numbers of travellers to each destination, sampling variation in the numbers of those answering was taken into account.

**4.1.4. RESEARCH CLEARANCES**

As this was a retrospective registry study based solely on a database without identification of any individual patient, no ethical approval was required. Instead, a research clearance was provided by SOS International.

## **4.2. STUDY II: CAUSES OF FEVER IN TRAVELLERS RETURNING FROM MALARIA-ENDEMIC AREAS**

### **4.2.1. MATERIAL**

The study subjects were travellers with fever admitted to the emergency room for internal and pulmonary medicine of Helsinki University Central Hospital (HUCH) between January 1, 2005, and March 31, 2009, after their trip to tropical or subtropical areas. Identification of these cases was retrospective, with a laboratory request for a malaria smear as a search tool; the first ten patients in each month were selected, and a total of 500 cases were collected. Adult patients ( $\geq 16$  years) with fever ( $>37.5^{\circ}\text{C}$ ) and a travel history to the tropics or subtropics within the previous year were included. The final analysis comprised 462 cases meeting these inclusion criteria.

### **4.2.2. DATA COLLECTION**

Methods and definitions are described in more detail in the original article. The following information was retrospectively collected from medical records: demographic data, detailed travel history, reason for travel, symptoms and their time of onset, chest x-ray and laboratory findings, antimicrobial treatment, diagnoses, and duration of hospitalization. The final etiological or clinical diagnosis of all patients, evaluated at least one year after discharge, was defined by H.S., who had access to all the results.

### **4.2.3. STATISTICAL ANALYSIS**

Chi-square tests, t-tests, and Mann-Whitney tests served to test for differences between groups. Binary and multinomial logistic regression models served to identify explanatory variables to the outcome variables. Variables found to have a p-value less than 0.2 were included in the multivariable models. To identify independent risk factors, forward and backward selection was with Akaike information criteria (AIC). For one variable (duration of trip), 72 values of the 462 were missing, and to take that into account in the model, we used multiple imputation with the assumption that the missingness process was missing at random (MAR). The analysis was carried out with SPSS 18.0.2 (SPSS Inc, Chicago, IL, USA).

#### **4.2.4. RESEARCH CLEARANCES**

The study protocol was approved by the Department of Internal Medicine of Helsinki University Central Hospital.

### **4.3. STUDY III: IMPORTED MALARIA IN FINLAND 1995–2008: AN OVERVIEW OF SURVEILLANCE, TRAVEL TRENDS, AND ANTIMALARIAL DRUG SALES**

#### **4.3.1. MATERIAL**

The study material included nationwide population-based surveillance data on malaria cases reported to the National Infectious Disease Register (NIDR) of Finland during 1995–2008. This information was related to data on travelling and antimalarial drug sales. Numbers of travellers were retrieved from the Official Statistics of Finland (OSF) and the Association of Finnish Travel Agents (AFTA). OSF data included information on overnight leisure trips to malaria-endemic countries during 2000–2008. AFTA data included annual numbers of organized trips during 1999–2007. The database of the Finnish Medicines Agency provided figures on antimalarial drug sales.

#### **4.3.2. DATA COLLECTED**

Methods and definitions are described in more detail in the original article. NIDR data included information on age, sex, nationality, date of diagnostic specimen, and country of infection. The National Population Information System provided additional data on country of birth and malaria-related deaths.

#### **4.3.3. STATISTICAL ANALYSIS**

Descriptive and time series analyses were performed, as was linear regression for trend analysis. Data were analyzed using Stata software, version 10.0 (Stata Corporation, College Station, TX, USA).

#### **4.3.4. RESEARCH CLEARANCES**

As this was a retrospective registry study based solely on a database, no ethical approval was required. Instead, research clearance was provided by the National Institute of Health and Welfare.

### **4.4. STUDY IV: IMPORTED MALARIA IN FINLAND 2003–2011: PROSPECTIVE NATIONWIDE DATA WITH RECHECKED BACKGROUND INFORMATION**

#### **4.4.1. MATERIAL**

We examined in detail the background information on all cases of imported malaria confirmed and recorded by the reference laboratory of Finland (population 5.4 million) between 2003 and 2011. We compared the cases with those reported to the National Infectious Disease Register. The information came from detailed questionnaires sent to the relevant clinicians upon diagnosis. H.S. sought missing data by use of telephone calls to the clinician or patient.

#### **4.4.2. DATA COLLECTION**

Methods and definitions are described in detail in the original article. The following data were collected: demographic variables (sex, age, country of birth, nationality, recent and earlier countries of residence, date of immigration); detailed travel history (countries and areas visited, dates, reason for travel); pre-travel advice received; use of chemoprophylaxis; symptoms; date of onset, first contact with healthcare, presentation at hospital and diagnostic specimen; malaria species; diagnostic method; date of commencing treatment; medication used for treatment; time and place of diagnosis, treatment and hospitalization; complications and outcome. In all cases of *P. falciparum* malaria with self-reported compliant use of antimalarials, we rechecked the compliance.

#### **4.4.3. STATISTICAL ANALYSIS**

Differences between various groups were tested by the chi-square test, student's t-test, or Mann-Whitney U-test, as appropriate. Statistical analyses were carried out with SPSS version 19.0 (Norusis; SPSS Inc., Chicago, IL, USA).

#### **4.4.4. RESEARCH CLEARANCES**

The study protocol was approved by and research clearance came from the Department of Internal Medicine of Helsinki University Central Hospital. The reference laboratory collected the information as part of its monitoring activity.

## 5 RESULTS

### 5.1. STUDY I: ILLNESS AND INJURY OF FINNISH TRAVELLERS ABROAD

#### 5.1.1. PATIENT CHARACTERISTICS

The analysis included 50 710 cases: 42 371 (83.6%) outpatients, 8 339 (16.4%) inpatients. Median age was 45 years, and 45.1% were men. Inpatients were more often men (52.2% vs. 43.7%,  $p<0.001$ ) than were outpatients, and were of higher median age (48 years, IQR 27–64, vs. 44 years, IQR 20–61;  $p<0.001$ ). Most of the cases, 36 699 (72.4%), occurred in Europe and the eastern Mediterranean. The country with the highest number was Spain with 18 583 (36.6%) cases, of which 13 435 (72.3%) were in the Canary Islands.

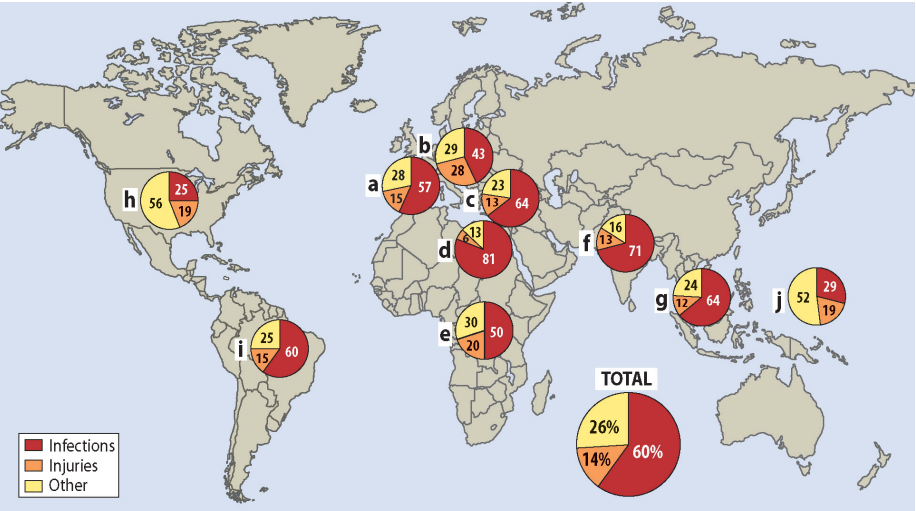
#### 5.2.2. DIAGNOSES

Infections represented the largest diagnostic category (59.9%), followed by injuries (14.0%), skin diseases (5.2%), musculoskeletal and soft tissue diseases (5.2%), diseases of the digestive tract (2.5%), and vascular diseases (2.1%). Infections and injuries were the largest diagnostic categories among both outpatients and inpatients. Proportions of infections and injuries of all diagnoses are presented in Figure 1 by geographic region. Skin-disease cases were most often treated as outpatients (99.0%), as were cases of musculoskeletal and connective tissue diseases (94.4%), whereas cases with vascular diseases were mostly treated as inpatients (65.9%).

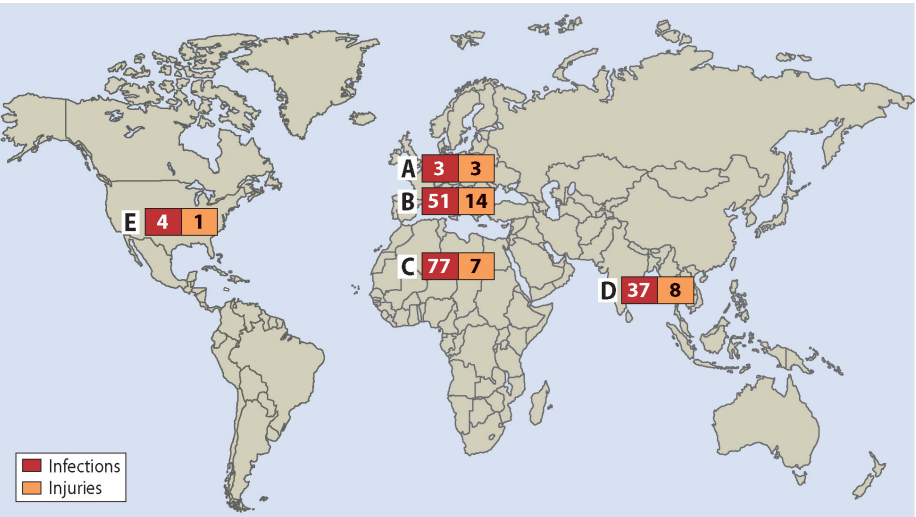
Acute gastroenteritis (11 543 cases) proved to be the most common single diagnosis and the most common type of infection (22.8% of all cases, 38.0% of infections, 20.9% of outpatients, 32.2% of inpatients). Respiratory tract infections (10 475 cases) were nearly as common (20.7% of all cases, 34.5% of infections, 23.0% of outpatients, 8.9% of inpatients). The other infection groups were: ear infections, 3 843 (12.6%), dermatologic infections, 1 538 (5.1%), urogenital infections, 1 311 (4.2%), eye infections, 955 (3.1%), systemic febrile infections, 673 (2.2%), and other infections, 55 (0.2%).

Injuries comprised 5 567 (78.5%) traumas and 1 528 (21.5%) other injuries. Of traumas, 4 270 (76.7%) were superficial traumas, 952 (17.1%) fractures, and 287 (5.2%) intracranial injuries.

Travel itinerary remained unchanged in 48 842 (96.3%), an air ambulance was necessary for 113 (0.2%), and another re-arrangement of transport for 1 556 (3.1%) cases. The number of deaths was 199 (0.4%).



**Figure 1**  
Percentages of infections and injuries of all diagnoses by geographic region



**Figure 2**  
Incidence of infections and injuries of adult travellers per 100 000 travel days by geographic region



### 5.2.3. INCIDENCE OF ILLNESS AND INJURY

The overall incidence of illness and injury was high in Africa (97.9/100 000 travel days; BCI 53.1–145.5), southern Europe plus the eastern Mediterranean (92.3/100 000 travel days; BCI 75.4–110.1), and Asia plus Oceania (65.0/100 000 travel days; BCI 41.5–87.9); the incidence was low in eastern plus western Europe (7.7/100 000 travel days; BCI 6.3–9.4) and the Americas (7.6/100 000 travel days; BCI 4.7–11.5) (Table 6). Incidence of infections was high in Africa, southern Europe plus the eastern Mediterranean, and Asia plus Oceania; incidence of injuries was highest in southern Europe plus the eastern Mediterranean and Asia plus Oceania (Figure 2). Of the individual countries available for comparison, overall incidence was highest in Egypt, followed by Turkey and Thailand, mainly due to acute gastroenteritis.

The study revealed a significantly higher incidence of illness and injury in southern Europe than in eastern plus western Europe. In southern Europe plus the eastern Mediterranean, the incidence was 5-fold higher for injuries and 17-fold higher for infections than in eastern plus western Europe. Comparison was possible between Portugal, Spain, Italy, Greece, and Turkey, and showed significant differences in incidences among them. In Italy and Portugal, overall incidence was similar to that of eastern plus western Europe. The incidence was highest in Turkey, attributable to acute gastroenteritis. Greece and Spain had the second and third highest incidences, mainly attributed to respiratory tract infections.

**Table 6** Incidence of health problems among adult travellers by geographic region and by country with >50 000 Finnish travellers/year

Adult Finnish travellers 2010–2012 <sup>a</sup>					Estimated number of travel days <sup>c,d</sup>		Incidence of illness and injury among adult travellers per 100 000 travel days <sup>e</sup>						
Regions and countries with more than 50 000 travellers/year <sup>b</sup>	Median age group (years)	Average duration of trip (days)	Number of travellers (n)	n	95% BCI	Overall	95%BCI	Infections	95%BCI	Gastro-enteritis	95% BCI	Respiratory infections	95% BCI
Eastern and western Europe	45-54	5.8	4 244 000	15 322 303	12 630 000-18 670 000	7.7	6.3-9.4	3.0	2.4-3.7	1.3	1.0-1.6	0.9	0.7-1.2
Germany	45-54	4.6	1 193 000	3 488 135	2 967 000-4 117 000	3.0	2.3-3.8	0.6	0.3-0.9	0.2	0.1-0.4	0.2	0.1-0.3
United Kingdom	35-44	7.4	798 000	3 717 048	2 409 000-5 618 000	0.9	0.5-1.4	0.2	0.1-0.4	0.0	0-0	0.1	0-0.3
France	35-44	5.3	596 000	1 998 866	1 548 000-2 590 000	5.4	3.8-7.3	0.8	0.4-1.3	0.5	0.2-0.8	0.1	0-0.3
Netherlands	45-54	4.7	278 000	862 565	577 100-1 271 975	2.0	1.0-3.4	0.1	0-0.5	0.1	0-0.5	0.0	0-0
Poland	45-54	6.5	246 000	986 757	453 100-1 929 000	1.8	0.6-3.8	0.5	0.1-1.2	0.0	0-0	0.2	0-0.8
Austria	45-54	6.1	237 000	898 087	703 300-1 147 000	13.9	10.1-18.5	0.9	0.4-1.7	0.6	0.2-1.2	0.2	0-0.7
Switzerland	45-54	3.6	189 000	411 127	326 900-517 900	14.1	9.7-19.5	2.0	0.8-3.7	0.3	0-1.0	0.8	0.2-1.8
Hungary	55-64	9.4	184 000	1 073 219	717 700-1 578 000	2.4	1.3-3.9	0.6	0.2-1.3	0.2	0-0.6	0.2	0-0.6
Belgium	35-44	1.8	159 000	177 066	115 600-264 700	11.9	6.1-20.5	1.8	0.4-4.7	0.6	0-2.4	0.6	0-2.4
Southern Europe and the eastern Mediterranean	45-54	9.5	3 970 000	29 069 515	24 130 000-35 220 000	92.3	75.4-110.1	50.6	40.7-60.4	16.2	13.4-19.2	21.4	17.4-25.4
Spain including Canary Islands	45-54	11.5	1 703 000	15 229 947	11 280 000-20 600 000	98.3	68.8-130.5	55.0	39.7-74.7	15.1	10.9-20.1	27.6	20.1-35.5
Spain excluding Canary Islands	45-54	9.3	867 000	6 206 151	4 753 000-8 096 000	67.9	50.9-91.3	31.7	23.2-42.0	7.2	5.3-9.6	16.1	11.8-21.3
Canary Islands	55-64	14.0	836 000	9 662 893	6 249 025-15 730 000	115.4	91.6-208.1	72.3	47.8-107.6	21.4	13.2-32.8	36.7	23.1-56.6

Adult Finnish travellers 2010-2012 <sup>a</sup>				Estimated number of travel days <sup>c,d</sup>		Incidence of illness and injury among adult travellers per 100 000 travel days <sup>e</sup>							
Regions and countries with more than 50 000 travellers/year <sup>b</sup>	Median age group (years)	Average duration of trip (days)	Number of travellers (n)	n	95% BCI	Overall	95% BCI	Infections	95% BCI	Gastro-enteritis	95% BCI	Respiratory infections	95% BCI
Greece	45-54	9.7	688 000	5 120 660	3 870 000-6 843 000	109.1	80.3-141.6	52.8	37.7-70.6	11.9	8.6-15.7	21.9	15.9-29
Italy	35-44	5.9	546 000	2 524 458	2 070 000-3 081 000	5.9	4.5-7.5	2.1	1.5-2.9	0.3	0.1-0.5	1.0	0.6-1.6
Turkey	45-54	8.2	418 000	2 635 836	2 076 000-3 351 000	212.1	162.4-264.6	127.4	97.9-161.4	67.9	52.5-85.3	30.2	22.9-38.3
Portugal	45-54	10.3	238 000	1 884 158	1 259 000-2 766 000	4.3	2.7-6.5	0.9	0.4-1.6	0.3	0.1-0.7	0.4	0.1-0.8
Asia and Oceania	45-54	18.6	955 000	13 270 311	8 932 000-20 680 000	65.0	41.5-87.9	37.4	23.8-53.5	20.6	14.2-29.5	8.9	5.9-13.0
Thailand	45-54	14.9	365 000	4 049 129	2 534 000-6 278 000	191.6	109.4-286.0	112.0	66.0-165.3	59.0	37.5-90.8	27.8	17.5-41.4
China	45-54	13.8	180 000	1 915 398	1 452 000-2 525 000	7.2	5.1-9.7	2.0	1.2-2.9	0.8	0.4-1.3	0.7	0.3-1.2
The Americas	35-44	18.5	511 000	7 218 042	4 574 000-10 950 000	7.6	4.7-11.5	3.5	2.1-5.3	1.8	1.1-2.7	1.0	0.6-1.5
USA	35-54	17.1	319 000	4 194 332	2 302 000-7 272 000	4.7	2.4-8.3	1.2	0.6-2.1	0.2	0.1-0.4	0.4	0.2-0.9
Africa	35-54	13.6	273 000	2 743 830	1 661 000-4 266 000	97.9	53.1-145.5	77.0	48.3-119.5	63.0	38.0-100.3	6.6	3.9-10.5
Egypt	35-44	9.7	132 000	1 016 085	605 300-1 547 000	249.1	158.2-393.7	197.9	114.7-308.1	184.6	110.6-290.5	18.6	10.7-29.8

<sup>a</sup>data from the Official Statistics of Finland: overnight leisure and business trips abroad; includes travellers 15-74 years of age 2010-2011, and travellers 15-84 years of age 2012<sup>b</sup>

<sup>b</sup>figures for Nordic and Baltic countries and Russia not presented here; incidences not comparable with other regions because proportionally more cases are covered by the Social Insurance Institution of Finland (Kela), and trips are shorter than to other regions

<sup>c</sup>number of travel days calculated as follows: average duration of leisure and business trips multiplied by number of travellers with travel insurance

<sup>d</sup>estimated proportion of travellers with travel insurance = 70%; source: Federation of Finnish Financial Services. Vakuutus tutkimus 2012

[insurance research 2012], available at: <http://www.fki.fi/materiaalipankki/julkaisu/Sivut/vakuutus tutkimus.aspx> [Last accessed February 20, 2014]

<sup>e</sup>incidence per 100 000 travel days = (number of cases handled by SOS International divided by number of travel days) x 100 000

BCI= Bayesian credible interval

## 5.2. STUDY II: CAUSES OF FEVER IN TRAVELLERS RETURNING FROM MALARIA-ENDEMIC AREAS

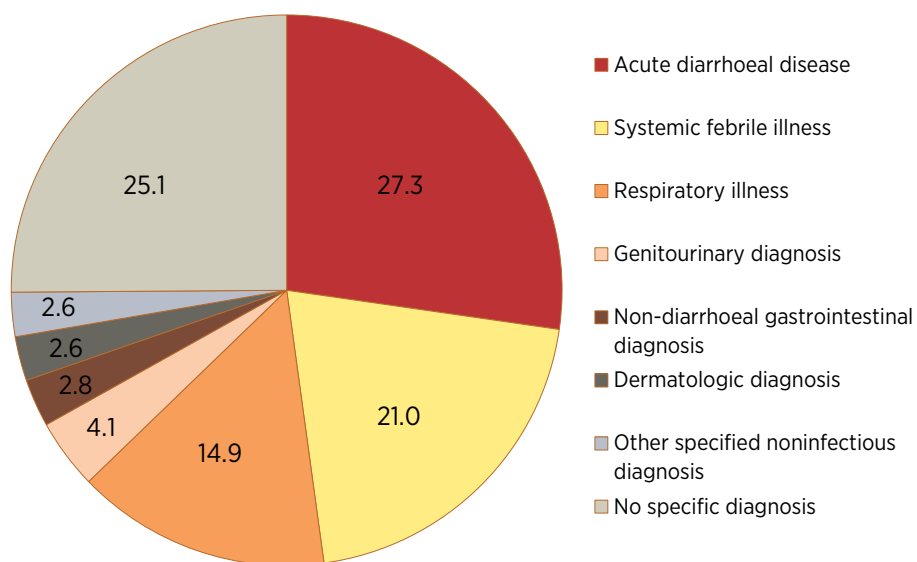
### 5.2.1. PATIENT CHARACTERISTICS

The study included 462 patients, of whom, 55% were men. Median duration of travel was 15 days (IQR 13–30). The regions visited most commonly were sub-Saharan Africa (42%), southeast Asia (28%), and central Asia plus the Indian subcontinent (20%).

### 5.2.2. DIAGNOSES

The most common main groups of diagnoses were: acute diarrhoeal disease (27%), systemic febrile illness (21%), and respiratory illness (15%). *Campylobacter* infection was the most common specific diagnosis (9%) and most common cause of acute diarrhoeal disease (32%). Malaria was diagnosed in 20 cases (4%). Blood culture was positive for bacteria in 21 cases (5% of the 428 tested): *Salmonella* species 5, *Escherichia coli* 3, *Salmonella paratyphi* 3, *Salmonella typhi* 2, *Staphylococcus aureus* 2, *Burkholderia pseudomallei* 1, *Klebsiella pneumoniae* 1, *Pseudomonas aeruginosa* 1, *Shigella sonnei* 1, *Streptococcus pyogenes* 1, *Streptococcus viridans* 1. Nasal swabs for influenza A and B antigen were positive in 7 cases (15% of the 47 tested); 111 cases fulfilled the criteria of influenza-like illness. HIV-antibody tests were run for 174 patients (38%) and proved positive in 5 (3% of those tested, 1% of all patients). A non-infectious disease was the cause of fever in 12 (3%); the reason remained unknown in 116 (25%) cases. More than one disease was diagnosed in 45 (10%). The proportions of the diagnosis groups are presented in Figure 3, and the diagnoses in detail in Table 7.

A potentially life-threatening illness was diagnosed in 118 patients (26%); the strongest risk factors were baseline CRP  $\geq 100$  (OR 3.6; 95% CI 2.0–6.4) and platelet count  $\leq 140$  (OR 3.8; 95% CI 2.0–7.3). Nine patients (2%) were treated in high-dependency or intensive-care units. Mortality was 0.2%, one patient died of *Pseudomonas* septicemia.



**Figure 3** Percentages of groups of final diagnoses of 462 returned travellers with fever

## RESULTS

**Table 7** Final diagnoses of 462 returned travellers with fever

Final diagnosis	1st diagnosis <sup>a</sup> n	2nd and 3rd diagnoses <sup>b</sup> n
<b>ACUTE DIARRHOEAL DISEASE</b>	<b>126 (27.3%)</b>	<b>20 (40.8%)</b>
Gastroenteritis NAS <sup>c</sup>	59	2
Campylobacter infection	40	5
Salmonellosis	15	5
Shigellosis	5	0
Yersiniosis	4	1
Giardiasis	2	3
<i>Clostridium difficile</i> infection	1	2
<i>Dieantamoeba fragilis</i> infection	0	2
<b>SYSTEMIC FEBRILE ILLNESS</b>	<b>95 (21.0%)</b>	<b>6 (12.2%)</b>
<b>Bacterial infections</b>		
Septicemia <sup>d</sup>	14	0
Unknown bacterial infection	8	0
Rickettsiosis <sup>d</sup>	6	0
Paratyphoid fever <sup>d</sup>	3	0
Typhoid fever <sup>d</sup>	2	0
Melioidosis <sup>d</sup>	2	0
Intra-abdominal abscess <sup>d</sup>	1	0
Leptospirosis <sup>d</sup>	1	0
<b>Viral infections</b>		
Dengue <sup>d</sup>	13	1
Acute viral infection	6	0
HIV infection <sup>d</sup>	4	1
<i>Epstein-Barr virus</i> infection	4	2
<i>Herpes simplex</i> infection	3	1
Epidemic nephropathy	3	0
Viral meningitis	2	1
<i>Cytomegalovirus</i> infection	1	0
HHV-6 infection	1	0
<b>Malaria</b>		
<i>P. falciparum</i> <sup>d</sup>	16	0
<i>P. vivax</i>	2	0
<i>P. ovale</i>	1	0
Species unknown	1	0
<b>Fungal infections</b>		
Pulmonary histoplasmosis	1	0

Final diagnosis	1st diagnosis <sup>a</sup> n	2nd and 3rd diagnoses <sup>b</sup> n
<b>RESPIRATORY ILLNESS</b>	<b>69 (14.9%)</b>	<b>9 (18.4%)</b>
Upper respiratory tract infection	26	3
Pneumonia <sup>d</sup>	22	5
Influenza	8	0
Legionnaires' disease <sup>d</sup>	1	0
Pulmonary tuberculosis <sup>d</sup>	1	0
<i>Pneumocystis jirovecii</i> pneumonia <sup>d</sup>	1	0
Atypical mycobacteria infection	0	1
<b>NON-DIARRHOEAL GASTROINTESTINAL DIAGNOSIS</b>	<b>13 (2.8%)</b>	<b>3 (6.1%)</b>
Viral hepatitis	2	1
Clonorchiasis	1	1
Other gastrointestinal diagnoses <sup>d,e</sup>	10	1
<b>GENITOURINARY DIAGNOSIS</b>	<b>19 (4.1%)</b>	<b>4 (8.2%)</b>
Pyelonephritis <sup>d</sup>	16	0
Acute urinary tract infection	2	3
Generalized gonococcal infection	1	0
Spontaneous abortion	0	1
<b>DERMATOLOGIC DIAGNOSIS</b>	<b>12 (2.6%)</b>	<b>3 (6.1%)</b>
Erysipelas <sup>d</sup>	8	0
Skin infection	3	2
Anaphylactic reaction <sup>d</sup>	1	0
Rash of unknown origin	0	1
<b>OTHER SPECIFIED NON-INFECTIOUS DIAGNOSIS</b>	<b>12 (2.6%)</b>	<b>4 (8.2%)</b>
Collagen disease	7	1
Sarcoidosis	2	0
Non-Hodgkin lymphoma <sup>d</sup>	1	0
Subacute thyroiditis	1	0
Mefloquine intolerance	1	0
Eosinophilia	0	1
Rabies exposure	0	1
Tension neck	0	1
<b>NO SPECIFIC DIAGNOSIS</b>	<b>116 (25.1%)</b>	
<b>ALL (N)</b>	<b>462</b>	<b>49</b>

<sup>a</sup>diagnosis regarded as the main cause of fever

<sup>b</sup>other new independent diagnosis

<sup>c</sup>causative agent remained unknown

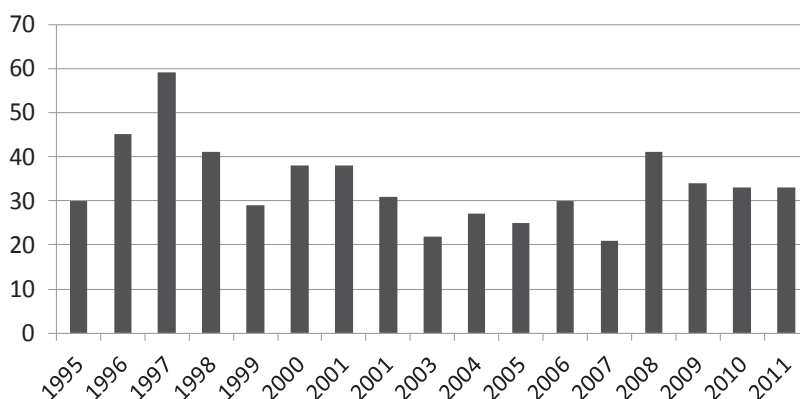
<sup>d</sup>disease potentially leading to death without specific or supportive treatment

<sup>e</sup>5 patients with potentially life-threatening illness: 3 pancreatitis, 1 cholangitis, 1 gastrointestinal bleeding

### 5.3. STUDY III: IMPORTED MALARIA IN FINLAND 1995–2008: AN OVERVIEW OF SURVEILLANCE, TRAVEL TRENDS, AND ANTIMALARIAL DRUG SALES

A total of 484 malaria cases (average annual incidence 0.7/100 000 population) were reported during the study period. The most common species diagnosed were *Plasmodium falciparum* (61%), and *P. vivax* (22%). Of these cases, 283 were Finnish-born and 201 foreign-born. Median age was 32 (range 0–80) years; 69% were men. Children comprised 15% of all cases; 72% of these were foreign-born, 28% Finnish-born. Infections were mostly acquired in Africa (76%). Among foreign-born cases, 89% of the malaria infections were acquired in the region of birth, mostly in Africa (106 cases). Three malaria-related deaths occurred during the study period.

Travel to malaria-endemic areas increased during the study period, but no rise occurred in the number of imported malaria cases. A decreasing trend appeared in antimalarial drug sales.



**Figure 4** Annual number of imported malaria cases in Finland, 1995–2011

### 5.4. STUDY IV: IMPORTED MALARIA IN FINLAND 2003–2011: PROSPECTIVE NATIONWIDE DATA WITH RECHECKED BACKGROUND INFORMATION

Annual numbers of imported malaria cases from 1995 to 2011 are presented in Figure 4.

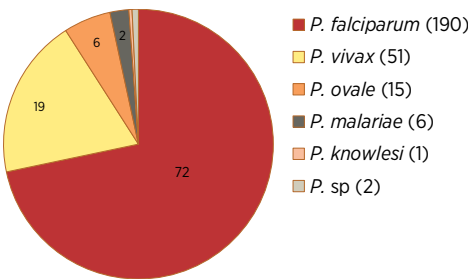
During 2003–2011, a total of 265 malaria cases (average annual incidence rate 0.5/100 000 population) were recorded by the reference laboratory; all of them were also reported to the NIDR. *Plasmodium falciparum* was the most common diagnosed species (72%) (Figure 5a). Most infections (81%) were contracted in



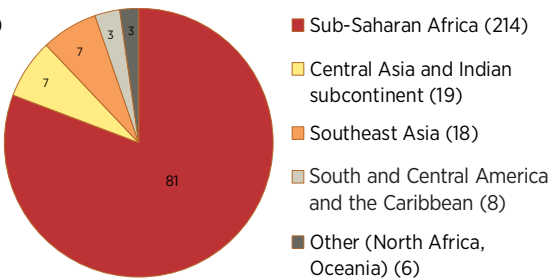
sub-Saharan Africa (Figure 5b). No malaria-related deaths were recorded during this study period.

Median age was 31 years (range 1–71); 71% were men. Of all cases, 144 (54%) were born in malaria-endemic countries, and 229 (86%) were currently living in Finland or in another non-endemic region. Immigrants visiting friends and relatives (29%) and Finnish residents travelling as tourists (25%) constituted the largest groups of travellers (Figure 6).

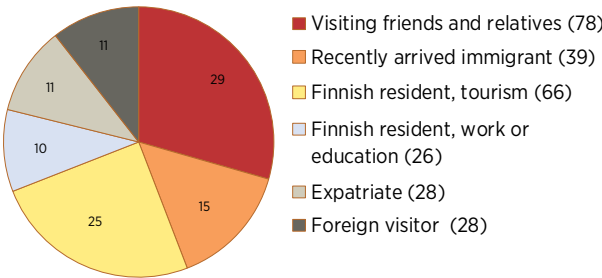
Pre-travel advice was received by 81% of those born in non-endemic regions, and 20% of those born in endemic regions. Regular use of appropriate malaria chemoprophylaxis was reported for 13 (5% of all cases), but for none of those born in an endemic area. Of those with *P. falciparum*, 4% reported regular use of appropriate chemoprophylaxis (atovaquone/proguanil or doxycycline or mefloquine for regions with chloroquine-resistant *P. falciparum*; atovaquone/proguanil or doxycycline for regions with mefloquine-resistant *P. falciparum*). After individual rechecking, however, none of them was found to have been fully compliant.



**Figure 5a** Percentages of *Plasmodium* species of the 265 imported malaria cases in Finland, 2003-2011



**Figure 5b** Geographic region for contracting malaria of the 265 imported cases in Finland, 2003-2011, by percentage



**Figure 6** Reason for travel of those importing the 265 malaria cases in Finland, 2003-2011, by percentage

## 6 DISCUSSION

In medicine and in research, travel medicine is a relatively new field. Escalating numbers of international travellers are expected to pose an increasing burden upon health care systems both in their destination countries during travel and in their home countries after return. Research data will aid in finding tools for preventive measures as well as for diagnostics and treatment of travel-related illnesses.

### 6.1. STUDY I: ILLNESS AND INJURY OF FINNISH TRAVELLERS ABROAD

The perception of travellers' health problems has relied on reports on relative morbidity, since the numbers of travellers to each region as denominator data to calculate the incidence have been unavailable.<sup>19</sup> Study I was built on an exceptional situation in Finland, which has two large databases available: one, that of a single assistance organization of insurance companies covering 95% of Finnish travellers using services of such organizations abroad, and the other of OSF, providing the numbers of Finnish travellers to various destinations. Combining data from these two sources made possible a nearly comprehensive nationwide analysis of relative morbidity for various diagnoses and made it possible to calculate incidences of illnesses and injuries during travel in individual geographical areas.

The data include no information on those not contacting any insurance companies/assistance organizations while abroad (either making a claim directly to the insurance company later or not using their insurance) or on those without travel insurance. Because the study material covers 95% of all Finnish cases abroad handled by assistance organizations, the data can be considered to represent quite comprehensively travellers' most serious health problems. One of the strengths of this study was the accuracy of diagnoses, since data came directly from clinicians treating the patient abroad.

As similarly suggested by prospective cohort studies,<sup>2,3,47,49–53,81,82</sup> infections clearly outnumbered all other health problems during travel. This was the case not only in developing countries, but also in southern Europe and the eastern Mediterranean. The proportion of infections proved higher than in previous studies based on data from assistance organizations (60 % vs. 20–40%),<sup>85–87</sup> probably because, instead of organ-specific categories, we included all infections in a category of their own. The most common infection and single diagnosis proved to be acute gastroenteritis (23%), consistent with earlier findings both on illness abroad<sup>2,3,15,33–37,47,49–53,81,82</sup>

and on returning travellers.<sup>2,4,74</sup> Respiratory infections were nearly as common as gastroenteritis (21%). Prospective studies have reported between 2% and 26% of travellers to have respiratory infections during travel,<sup>2,3,47,49–53,81,82</sup> and sentinel-surveillance studies have shown between 8% and 11% of their patients with respiratory disease after travel.<sup>4,68,74,117</sup> The latter report mainly cases in specialized tropical and travel medicine centres, while patients with post-travel respiratory symptoms probably seek help in primary care.

As in other studies on health problems during travel,<sup>2,86</sup> systemic febrile infections proved uncommon, and were markedly less frequent than in post-travel sentinel surveillance reports.<sup>4,68,70,74</sup> The latter studies report malaria as the most frequent cause of systemic febrile illness in travellers.<sup>4,68,74,148</sup> Our study, assumed to cover the most serious cases of illness, showed malaria to be rare during travel (8 cases, 3.5% of systemic febrile illnesses). Interestingly, the proportion of dengue (84 cases, 35.0% of systemic febrile illnesses) was higher than reported in returning travellers (10–15% of systemic febrile illnesses).<sup>68,74</sup> During the study period, 85 imported cases of malaria and 190 of dengue were diagnosed in Finland<sup>251</sup>; thus, dengue symptoms seem to begin during travel more often than do those of malaria, consistent with dengue's shorter incubation period. TD and respiratory infections have short incubation periods as well, which contributes to their high frequency during travel. As TD usually is a spontaneously resolving disease, and mild respiratory tract infections do not always lead to contact with health care providers, the proportion of those infections, although large in our study, probably still represents an underestimation of their real burden on travellers.

Many papers, such as GeoSentinel surveillance studies,<sup>68</sup> have reported differences in relative morbidity between regions. In prospective cohort studies, the region with the highest relative morbidity has been dependent on the travel destinations of the study populations: *e.g.* either West Africa,<sup>3</sup> the Indian subcontinent,<sup>2,52</sup> or the Middle East and Latin America.<sup>53</sup> One Swedish study<sup>49</sup> reported the highest attack rates of diarrhoea in travellers to northern Africa and the Indian subcontinent, followed by sub-Saharan Africa; a Swiss report<sup>50</sup> in travellers to south Asia, followed by Latin America, southeast Asia, and sub-Saharan Africa. Our study gives incidences of illness and injury allowing comparisons between the various regions. The overall incidence proved high in Africa and, surprisingly, also in southern Europe plus the eastern Mediterranean, as well as Asia and Oceania. While the incidence of infections was high in Africa and Asia, it proved high also in southern Europe plus the eastern Mediterranean, 17-fold higher than in eastern plus western Europe. The profile of infections in southern Europe differed, however, from that in developing countries: instead of acute gastroenteritis, the incidence was highest for respiratory tract infections.

In Spain, overall incidence was higher in the Canary Islands than on the mainland, which is partly explainable by the travellers' higher median age and longer trip duration. Within southern Europe, we found between countries significant differences not solely explained by trip duration or traveller age. Although a low risk for gastroenteritis has been reported in southern Europe,<sup>80</sup> our study indicated elevated incidences in Greece and Spain. As also shown by others,<sup>4,82</sup> our study revealed that travelling within Europe is not without risk. This study showed that pre-travel counselling is needed also for travel to southern Europe.

These results provide tools for destination-specific risk assessment, travel counselling, and post-travel evaluation. This study shows that pre-travel advice should focus not only on safe food and drink abroad, but also on good hand hygiene for prevention of gastrointestinal and respiratory infections. Improved means for prevention of gastrointestinal and respiratory infections in travellers are needed.

## 6.2. STUDY II: CAUSES OF FEVER IN TRAVELLERS RETURNING FROM MALARIA-ENDEMIC AREAS

Study II was designed to find the causes of travel-related fever after a journey; the data were expected to provide tools for diagnostics and treatment. We used the disease classification of GeoSentinel.<sup>147</sup> Our data represented patients in an emergency department of a main tertiary referral hospital, whereas GeoSentinel sites are centres of tropical and travel medicine. We found equal proportions of respiratory illnesses (15% vs. 14%), but more acute diarrhoeal diseases (27% vs. 15%) and less systemic febrile illness (21% vs. 35%), suggesting that the GeoSentinel patient material<sup>147</sup> has been more selected.

Malaria has been reported as the most frequent cause of fever without localizing symptoms in returning travellers in other hospital-based<sup>26,27,94,98–102</sup> and sentinel-surveillance<sup>4,68,74,147</sup> studies. Although the most commonly visited region in our study population was sub-Saharan Africa, similar to most other studies (42% vs. 34–86%),<sup>4,27,68,98–102,147</sup> we found malaria in only 4%, as compared with 21 to 75% in the other studies,<sup>26,27,94,98–102,147</sup> suggesting their more selected material.

We took blood cultures from 93% of patients, and septicemia proved as common as malaria (5% vs. 4%). In most similar studies, a septicemia diagnosis has not been sought.<sup>27,94,100,102,147</sup> In those reporting it, the rate of septicaemia has ranged from 0.1 to 2%, yet blood cultures had not been run routinely from all of those patients.<sup>26,98,99,101</sup> In one Italian study,<sup>99</sup> blood culture was done for 56%, and found positive in 10% of them.

In one GeoSentinel series in which 91% of patients had fever, an acute and potentially life-threatening tropical disease was diagnosed in 4.4%<sup>5</sup>; in our study,

5% of returned travellers with fever fulfilled the same criteria. Another definition: that of a disease potentially leading to death if left without specific or supportive treatment was met by 26% of our patients, suggesting that the referral criteria had been correct.

Nasopharyngeal swabs for influenza A and B antigen proved positive in 15% of those we tested; yet swabs were taken from only 42% of those retrospectively evaluated to have fulfilled the criteria of an influenza-like illness. This supports the findings of earlier studies based on serology<sup>142,150</sup> suggesting influenza in travellers to be under-diagnosed. Influenza is the most common vaccine-preventable disease of travellers<sup>142</sup> and should be considered in the differential diagnostics of febrile travellers also outside the epidemic season of the northern hemisphere.

A new HIV diagnosis was established in 3% of the 174 tested, 1% of all our patients. Other studies have reported newly diagnosed HIV infections in 0.3 to 1.5% of febrile returned travellers, yet not all patients had been tested.<sup>26,98–102</sup> A GeoSentinel study reported sexually transmitted disease (STD) in 0.9% of ill travellers; HIV was diagnosed in 2% of all those presenting after travel.<sup>252</sup> HIV infection has been the diagnosis for 4% of returned travellers presenting with mucocutaneous signs suggesting a STD,<sup>253</sup> 3% of those with fever and exanthema,<sup>254</sup> and 7% of those with infectious mononucleosis-like syndromes.<sup>255</sup> In these studies, too, patients had not been systematically tested for HIV. The Centers for Disease Control and Prevention in the USA (CDC) recommends offering routine HIV-testing for everyone in contact with health care in populations where the prevalence of HIV is >0.1%.<sup>256</sup> Therefore, it seems justified to recommend HIV tests for all travellers returning ill.

The cause of fever remained unknown in 25% of cases, similar to other studies' findings (5–24%),<sup>26,27,94,100–102,147</sup> all of them with a benign course. Mortality corresponded to that in other reports (0.2% vs. 0.2–0.5%).<sup>94,101,147</sup> Non-infectious diseases were the cause of fever in 3% of our patients, compared to 0 to 5% in other studies.<sup>26,27,98–102</sup> One patient in ten had more than one separate diagnosis, similar to figures in other reports (10–16%),<sup>98,99,101</sup> showing the importance of careful diagnostics in returning travellers with fever.

### 6.3. STUDIES III AND IV: MALARIA

All malaria cases diagnosed in Finland are imported; autochthonous malaria has not appeared in Finland since the 1950s.<sup>237</sup> Although under-reporting of imported malaria cases occurs in Europe,<sup>238</sup> it seems that no under-reporting occurs in Finland: the same individual cases were identified annually in the notifications to the National Infectious Disease Register and in the data of the reference laboratory both in Study III and in Study IV.

### 6.3.1. STUDY III: IMPORTED MALARIA IN FINLAND 1995–2008 AN OVERVIEW OF SURVEILLANCE, TRAVEL TRENDS, AND ANTIMALARIAL DRUG SALES

Study III compared malaria notification data, travel statistics, and malaria chemoprophylaxis drug sales during 1995–2008. Travelling to malaria-endemic areas increased during the study period, yet no increase occurred in the number of imported malaria cases except for a peak in the last quarter of 2008 due to a cluster of travellers to the Gambia.<sup>257</sup> Asia is the tropical area most favoured by Finnish travellers,<sup>6</sup> yet the majority of our malaria cases were acquired in sub-Saharan Africa, correlating with the highest incidence of malaria in this region.<sup>155</sup> The increase in number of trips was mostly to areas with limited risk, which may in part explain why the number of malaria cases remained stable. On the other hand, it may also reflect a decreasing malaria risk for travellers in endemic areas as is reported from Latin America,<sup>258</sup> West Africa,<sup>259</sup> India,<sup>250</sup> and southeast Asia.<sup>260</sup>

Sales of drugs for malaria chemoprophylaxis decreased after 1997, and then began to increase slowly from 2005 onward, coinciding with atovaquone/proguanil coming onto the market. Notably, although included in the Finnish guidelines for malaria chemoprophylaxis, doxycyclin was not included in our analysis, since it is used mainly for other indications. Data on drug sales may thus be misleading, and the decrease observed in the sales of other drugs may be due to a respective increase in the doxycycline sales. A decreasing trend for antimalarial drug sales can be explained also by other factors, such as travellers' under-estimation of risk for malaria,<sup>41</sup> their fearing adverse drug reactions<sup>215</sup> or their purchasing the drugs only at their destination.<sup>208</sup> Moreover, compliance with antimalarials is reportedly low.<sup>49,57,214,216,217,219–222</sup> Thus antimalarial drug sales alone fails to allow estimation of chemoprophylaxis use.

Approximately 40% of the malaria cases occurred among foreign-born individuals; 90% of them were VFR travellers, most frequently those born in Africa — the most common region for contracting the disease. These data are in line with other European findings.<sup>188,241–249</sup> Children constituted 15% of all and more than one-quarter of foreign-born cases, similar to others' figures.<sup>106</sup> Children reportedly comprise from 11 to 23% of all imported cases of malaria, with the majority of their infections being acquired in sub-Saharan Africa, and with a larger proportion of children than adults as being VFR (50–84%).<sup>106</sup> VFR children more often have symptomatic malaria and have higher parasite density than do recently arrived immigrant children, who have some partial immunity.<sup>261</sup> Children are at higher risk of developing complicated disease: 5 to 10% of children with imported malaria have had severe cases.<sup>262</sup> Our study confirmed that immigrants visiting friends and relatives in their country of origin, especially children of immigrant families, are at high risk for malaria. More effort should focus on disseminating pre-travel advice to this risk group.

### **6.3.2. STUDY IV: IMPORTED MALARIA IN FINLAND 2003–2011 : PROSPECTIVE NATIONWIDE DATA WITH RECHECKED BACKGROUND INFORMATION**

Study IV analyzed in detail background information on imported malaria cases in Finland from 2003 to 2011. Distribution of age, gender, malaria species, duration of travel, geographic regions, and risk groups were in line with other European figures.<sup>188,241–249,263</sup> No malaria-related deaths occurred in Finland during this period.

Immigrants constituted 117 (44%) of all cases: 29% were VFR travellers, and 15% recently arrived immigrants. Our study confirmed that VFR travellers are a risk group: they received less pre-travel advice than the Finnish-born cases, and none took appropriate chemoprophylaxis regularly. The proportion of VFR travellers has been large also in several other European reports.<sup>188,241–249,263</sup> Adult VFR travellers have been less likely to seek pre-travel advice and use effective malaria prophylaxis than are non-VFR travellers,<sup>115</sup> and VFR children use chemoprophylaxis even less frequently.<sup>262</sup> Lack of malaria prophylaxis has been suggested to be due to a lack of knowledge of malaria transmission and prevention,<sup>214,264,265</sup> and erroneous trust in lifelong immunity.<sup>113,116,199</sup> VFR travellers may be more heavily exposed to malaria than others since they frequently visit rural areas and often during the rainy season.<sup>116</sup> Partial immunity developed while growing up in highly endemic areas wanes with time and no longer protects the adults from clinical malaria, yet it may protect from fatal complications. Consistent with other reports,<sup>174,189–191</sup> in our study those born in malaria-endemic regions had fewer complications than did those born in Finland or other non-endemic countries. The non-immune children of immigrant families are at greatest risk for symptomatic and severe malaria.<sup>79,116,266</sup> Pre-travel advice should thus be actively offered to immigrants during every contact they have with health-care services, whenever plans to travel to malaria-endemic country emerge.

Finnish travellers with malaria proved not to have taken appropriate chemoprophylaxis, even though having received pre-travel advice. Despite the fact that national guidelines are easily available,<sup>205</sup> in five cases the physician had incorrectly advised against chemoprophylaxis and in 19 cases the drug prescribed was inappropriate. This highlights the importance of continuous training of health-care professionals. In nine cases, the traveller had bought inappropriate over-the-counter drugs at the destination. Pre-travel advice should emphasize the dangers of buying drugs in endemic countries, as such may not only provide inappropriate chemoprophylaxis, but may also be counterfeit drugs.<sup>267</sup>

No doctors' delay occurred from presentation at hospital to diagnosis or the start of anti-malarial treatment; it thus seems that Finnish doctors working in hospitals are familiar with guidelines on diagnostics and treatment of malaria<sup>268,269</sup> and suspect malaria in febrile returning travellers. Most malaria patients were treated as inpatients, in accordance with European guidelines.<sup>167</sup> The median length of hospital stay was five days, similar to that in other European surveys.<sup>243,246,263</sup> Length

of hospitalization decreased during the study period, reflecting a change in treatment guidelines: since 2010 uncomplicated malaria has been treated with ACT (oral artemether/lumefantrine) instead of quinine plus doxycycline. Subsequently, in 2010, the hospital stay decreased to four days, and, in 2011, further to three days.

Cases of *P. falciparum* malaria have occurred despite reported appropriate chemoprophylaxis<sup>188,241,245–247,263</sup>; this information has been recorded, however, without reconfirmation of compliance. Adherence to chemoprophylaxis is difficult to assess in data based on questionnaires only,<sup>188,241,248,263</sup> with self-reported adherence higher than it is in actuality.<sup>223,270</sup> The question remaining is whether significant clinical resistance exists to drugs currently used for chemoprophylaxis. In our study, 4% of patients with *P. falciparum* malaria reported taking appropriate chemoprophylaxis regularly. When this was rechecked, all of them, however, admitted having been non-compliant. This study demonstrates that information on compliance may be unreliable, and such information should undergo a recheck in all cases of malaria. These results suggest that mefloquine, atovaquone/proguanil, and doxycycline are effective as chemoprophylaxis against *P. falciparum* malaria, when taken conscientiously.



## 7 CONCLUSIONS AND FUTURE PROSPECTS

Means for prevention of gastrointestinal and respiratory infections in travellers call for development; the data show a need for vaccines against enteric pathogens. Immigrants visiting friends and relatives in their country of origin, especially children of immigrant families, are at high risk for contracting malaria; more effort should focus upon dissemination of pre-travel advice to this group. Atovaquone/proguanil, doxycycline, and mefloquine seem effective as chemoprophylaxis against *P. falciparum* malaria, but travellers should take these conscientiously.

Although gastrointestinal and respiratory infections proved the most common health problems, malaria and other potentially life-threatening illnesses should continuously be emphasized because of their serious nature if left undiagnosed and untreated. In a tertiary hospital, fever without localizing symptoms in a traveller returning from malaria-endemic area should require a diagnostic protocol that, in addition to malaria smears, includes blood cultures, an HIV test, and an influenza rapid diagnostic test.

The database of an assistance organization of insurance companies proved a unique and valuable source of information on illness and injury diagnosed during travel. More detailed data are necessary, however, as to reason for and length of travel, travel itinerary, reason for injury, length of hospital treatment, and transportation of those fallen ill or injured abroad. This would prove useful both for development of assistance services and for planning of preventive strategies. The malaria surveillance system in Finland needs improvement: important background information resides in an additional register, but is missing from the main register and should be linked to it.

With expanding travel and migration, health professionals will increasingly be faced with health problems related to travel. Research and resources in this field will aid in development of prevention, diagnostics, and treatment. European and international cooperation is essential in surveillance of, research into, and establishment of guidelines on illnesses and injuries of migrants and travellers.

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